Endocrinology

The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

July, 1923

PROGRESS IN THE PREPARATION OF PANCREATIC EXTRACTS FOR THE TREATMENT OF DIABETES*

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Seldom does science—medical science in particular—advance in perfectly straight lines, or by perfectly logical steps one directly above the other. In ascending the mountain of knowledge as in ascending physical mountains progress more often is accomplished by a zig-zag course. At times a mountain trail may seem to have lost the habit of ascending; it may even recede toward lower levels. And it is only by patiently threading one's way through obscuring growths at the base of the mountain, and then ofttimes after further baffling experiences in fogs about the higher levels, that one emerges finally to the clearer view and the immediate consciousness of achievement. Such has been the progress of understanding in the treatment of diabetes.

Not for a third of a century—not indeed since the demonstration by Minkowski and von Mehring (1) in 1889 that the seat of the disease is in the pancreas—had there been any really great advance in the rational treatment of this malady until about a year ago. The promise of Minkowski's work was instantly recognized and hopes were everywhere entertained that

*Read before the Hennepin County Medical Society, Minneapolis, Minn., April 17, 1923.

complete mastery was at hand. Encouraged by the results with dried thyroid substance or extract in the treatment of myxoedema, it was believed that administration of pancreatic substance must bring relief in the treatment of diabetes. But the Minkowski contribution only got us out of the woods; we were still a long way from the summit and apparently insurmountable barriers interposed. There were not wanting many who caught, or thought they caught, glimpses of a sure passage over the difficulties. But many of these glimpses proved wholly illusory; most of the passages had to be abandoned completely.

A year ago the medical and scientific world was thrilled by the announcement from Toronto (for reasons which will appear more clearly as I proceed one of us localized this thrill very near the solar plexus) to the effect that the internal secretion of the pancreas had at last been obtained in curative form and in quantity sufficient to control the major symptoms both of experimental and spontaneous diabetes. Minkowski and von Mehring's discovery had been based upon the complete extirpation of the pancreas from dogs, producing thereby a fatal condition alike in all essential respects to the disease in man. Banting and Best's (2) discovery was based upon ligation of the pancreatic ducts in the dog, thereby producing degeneration of the acinous tissue of the organ and rendering possible the extraction of the anti-diabetic substance produced by the islet cells in a state of purity and potency never previously attained.

As in mountain climbing, so in scientific pioneering the surest progress often is made by following up as far as it goes a trail blazed by somebody else. Failures may show up along the way, mistakes which appear utterly foolish in the light of newer experiences. This one has gone off on the wrong branch; that one has followed a false lead. But eventually comes along a bolder spirit or one of surer instinct, or, it may be by pure chance, the new wayfarer hits upon the right clue and amazingly and triumphantly he leads the way toward the summit. This is what Banting has done. If it be chance, however, which brings success, we must remember that "chance" in the words of Pasteur, "favors only the mind which is prepared." Nobody succeeds wholly by chance and nobody succeeds only because his mind is prepared. Pasteur himself illustrates the importance of another element, namely, persistence; and this quality is well

exemplified also by Banting, who labored against discouragements for many months before he succeeded in convincing others that he was on the right track.

It is a mistake to suppose that some progress had not been made before this time—that pancreatic extracts had never been prepared or that they had not been used with some success on human cases. It is no discredit to Banting and his colleagues, rather the contrary, to recall that more than a dozen scientific investigations had been carried out with pancreatic material which diminished the excretion of sugar in either depancreatized dogs or human cases of severe diabetes or both before these investigators reported success. In several instances these preparations caused the complete disappearance of sugar from the urine, caused increase in weight, and general improvement in the clinical condition of the patient. But most of these attempts had to be abandoned because of toxic or other deleterious results which overshadowed the benefits gained.

Because we often learn more from a failure than from a success let me review *briefly* the history of these researches. Minkowski (3) himself, the next year after the publication of his completed experiments on extirpation in 1892, tried to make an extract of dog's pancreas which, when injected into the animal from which it had been taken would restore his power to metabolize sugar. He failed completely. Even before Minkowski, but stimulated by his discovery, Caparelli (4) made an extract of dog's pancreas in 0.76% NaCl solution which, when injected into the peritoneal cavity of a dog caused an abrupt fall in the excretion of sugar within three hours and in most instances complete disappearance soon thereafter. In 1893 also, clinical trials of pancreatic material were made by Ballistini (5) in Italy, and by Ralfe (6), Sibley (7), Wood (8), Mackenzie (9) and White (10) in England. Ballistini, Sibley and Ralfe reported some success; the others reported failures. Some of them gave fresh pancreas or pancreas slightly cooked, by mouth, some gave press juice and some extracts. In 1895 there were positive reports by Ausset (11) in France, and Bormann (12) in Russia, negative results by Vanni and Burzagli (13) in Italy. Ausset used raw pancreas of veal upon a depancreatized dog and a single human subject. Bormann used roast pancreas by mouth, later rectal infusions, and finally subcutaneous injections of raw

pancreas. One of his patients who received 1.5 cc. of pancreatic extract daily under the skin gained eight pounds in six weeks, the diet remaining substantially the same. Vanni and Burzagli used a glycerine extract and also raw pancreatic extract given subcutaneously. There was no clearly favorable result.

In 1896 there was one report upon each side of the controversy. Lisser (14) reported from Odessa that rectal infusions made from hashed fresh pancreas with normal saline solution caused marked diminution both of the glycosuria and polyuria. One subject gained 2.5 kgm. in weight, the other 4 kgm.; but in the latter case the infusions could not be tolerated longer. Spillmann (15) reported two subjects treated by injection with pancreatic press juice. There was only slight abatement of the glycosuria.

In 1897 Thesen (16) and Lauritzen (17) found favorable effects in human cases, the former feeding 50 to 300 gms. of raw pancreas daily, the latter a glycerine extract given by mouth. Thesen found, as many others have found since, that raw pancreas soon becomes repugnant. This year also a notable piece of work was done by Hougounenq and Doyon (18) upon depancreatized dogs. They made extracts in a great variety of ways, but were not able to demonstrate any beneficial effects when they were administered to the diabetic dogs by stomach. This well-controlled work made a marked impression on clinicians and very considerably discouraged the use of pancreatic material in any form by mouth; particularly as it was followed the next year by the observations of Hédon (19) to the effect that glycerine extract given by mouth to depancreatized dogs likewise produced almost no effect. Blumenthal (20), however, saved the record for 1898 by squeezing out the juice from raw pancreas in much the same way, though not employing such high pressures, as Buchner had used in obtaining zymase from yeast. He precipitated the proteins from this juice with alcohol and gave the filtrate to animals as well as to human subjects. Given intravenously it killed his animals but caused only necrosis at the site of injections when given subcutaneously either to animals or men with fatal diabetes. In one case he reports 40 per cent increase in the combustion (meaning utilization) of sugar. It is obvious why he discontinued its use. Nevertheless Blumenthal was on the right track.

Another significant observation this year (1898) was that of Lépine and Martz (21), who examined the lymph of a normal dog and found a substance capable, when injected intravenously into a rabbit, of causing marked glycolysis, i. e., disappearance of sugar from its blood. Although Lépine's idea of a ferment (glycolysin) later proved unacceptable, Biedl and Offer (22) several years later confirmed the significance of his observation on the thoracic lymph by showing that exclusion of the duct lymph from the circulation by ligation or by fistula produced profound glycosuria.

With one exception (23) all attempts (24, 25) made in the next ten years resulted negatively. In 1903 Rennie (26) reported upon the interesting occurrence of an entirely separate pancreatic organ for internal secretion in teleostean fishes, and four years later Rennie and Frazer (27) undertook the treatment of diabetes mellitus by feeding this islet material, but without avail. Lépine is the only outstanding worker who seemed never to lose faith in the ultimate solution along the lines of his glycolytic ferment. He believed the pancreas produced a substance (ferment) which it gave off mainly to the lymph rather than the blood, and that this ferment was the *sine qua non* for the breakdown of sugar, the absence or failure of which produced diabetes. Here should be mentioned the observations of Cohnheim (28) confirmed by Hall (29) upon the disappearance of sugar in vitro when pancreatic extract together with muscle plasma was allowed to act upon it at incubation temperature. Cohnheim at first thought this was a true oxidation, but Levene and Meyer (30) proved that the loss of reducing power was due to a process of polymerization; for all of the sugar could be recovered when the mixture was hydrolyzed with hydochloric acid.

Meantime by a process of attrition rather than by direct assault another important vantage point was gained. Observations were accumulating which rendered more and more probable the causal relation of the islet tissue to diabetes, first enunciated by Laguesse (31). Atrophy of the acinous tissue without change in the islets produced by ligation of the ducts, was first noted by Vassale (32) and was confirmed among others by Schultz (33), Ssobolew (34), Sauerbeck (35), Tiberti (36), Kirkbride (37) and Kamimura (38). Pathological changes in the

islet cells in cases of human diabetes have been described by Opie (39), Ssobolew (34), Herzog (40), Weichselbaum and Stangl (41), Gutman (42), Cecil (43) and others. While there is no unanimity of opinion as yet regarding the evidence from pathological material, the recent experiments of Allen (44) upon partially depancreatized dogs with production of hyaline degeneration in the B cells of the islets, coincident with a breakdown of carbohydrate tolerance, appear to place the dependence upon surer grounds.

This period from 1898 to 1908 was marked also by the development of the dietary treatment of diabetes and by the inauguration of almost endless researches upon the metabolism of diabetes which have by no means exhausted the subject even yet. The salient points for our present purpose established by these investigations are the following: (1) The primary defect in diabetes is not the excessive production of sugar but the inability of the organism to oxidize it. (2) This condition is signalized ordinarily by the attainment of a certain ratio (3.65 of glucose to 1 of nitrogen in the urine, the glucose being in excess of the glucose equivalent ingested); also by the attainment of a respiratory quotient of 0.69. (3) To attain these numerical levels the diabetic excretes all the sugar which is formed in the course of the metabolism of protein (as well as all his carbohydrate) and this amounts to as much as 60 per cent of its weight. (4) There is an excessive heat production in diabetes which is caused by the increased metabolism of protein. (5) The acidosis of diabetes arises from the inability of the diabetic to complete the oxidation of fatty acids and certain amino acids, with the result that these acids are excreted (aciduria) but especially also they deplete the reserves of alkali in the body (true acidosis). (6) Much information has been gained in recent years also upon the blood sugar in diabetes, its relation to sugar excretion, to dietary and starvation treatment, etc. So that we have today three main chemical criteria as to the condition of a diabetic: (1) the D:N ratio in the urine, first insisted upon and developed by Lusk; (2) the blood sugar level, standardized for the normal individual mainly by Benedict at Cornell, Folin at Harvard and Shaffer at St. Louis, and turned to account in the study of diabetes chiefly by Joslin at Boston, by Woodyatt at Chicago, and by Allen at Morristown,

and (3) the respiratory quotient first established for the diabetic by Magnus-Levy and confirmed by Kramer and myself for the dog and by DuBois and by Boothby for man. It may be mentioned in passing that the respiratory quotient is much more difficult to establish than the other criteria, and it is correspondingly more difficult to demonstrate a change in the respiratory quotient when any treatment for diabetes is being given. At the same time it is the best criterion of all of real improvement: *for unless you have restored your patient's capacity to oxidize glucose you have done him no permanent good.*

But to resume the story of the development of pancreatic therapy: Pflüger, in his famous controversy with Minkowski regarding the nature of diabetes, laid down the principle that an internal secretion is not proved by extirpation alone. One must be able also to restore lost function by administration of the organ substance, as was known even at this time for the thyroid, or an extract of the organ as in the case of the adrenals. Zuelzer (45, 46), in 1908, guided by this principle, and impelled by the belief that previous attempts with pancreatic material may have failed because of the condition of the pancreas at the time of extraction, made a very determined effort to prepare from perfectly fresh material an extract which should exhibit anti-diabetic properties and thereby to establish the fact that the pancreas accomplishes its work by means of a hormone. The term "hormone," by the way, had been introduced only a couple of years before by Bayliss and Starling in connection with their work on secretin. Zuelzer's efforts were all but successful. He took pancreas at the height of digestion, tied it off for an hour and a half, then removed and extracted it, squeezed out the juice, precipitated the proteins by means of alcohol, until there was scarcely any biuret reaction left, and administered the alcohol-free extract subcutaneously and intravenously. With depancreatized dogs he saw the sugar excretion fall off sharply or disappear. He reports eight human cases treated. Several of the subjects were obviously improved as regards excretion of sugar. One became sugar free, in spite of 100 grams bread in the diet, and remained so for four days from a single injection of 10 cc. of the extract. One of his cases was that of a boy six years of age who received a single injection of 5 cc. by vein. The urinary sugar dropped from 4.4% to 2.6% and both diacetic

acid and acetone disappeared from the urine. The child, however, showed a marked temperature reaction and was severely nauseated. For these reasons, apparently, the treatment was discontinued. Zuelzer's results, however, were confirmed the next year, 1909, by Forschbach (47), who published results on several depancreatized dogs and in some half-dozen human cases. Like Zuelzer, he was discouraged by febrile reactions.

Many times in the search for a satisfactory pancreatic therapy it has been reported (48, 49) that, so far from controlling diabetes, fresh pancreatic material aggravated the glycosuria. Leschke (50) in 1910 investigated the cause of this phenomenon which he had observed in frogs, by administering aqueous pancreatic extract which had been heated to 70° C. *for the purpose of destroying the external enzymes.* The heated material did not have the effect which he had seen with raw extracts. The latter in mammoth doses even caused glycosuria in normal animals. He concluded that the enzymes were responsible for the unfavorable effects. Allen (51) has shown that the glucosuric effect of pancreas extract injected in this way is not specific but is shared by other organs such as liver and skeletal muscle. Curiously enough Leschke thought his observations refuted the whole conception of an internal secretion, and he was so biased in this preconception as to be quite unfair in his review of results obtained by previous investigators. Allen seemed ten years ago to have borrowed Leschke's views.

Without doubt one cause for the many failures to produce a satisfactory extract up to this time had been the destruction of the hormone by the external enzymes (trypsin) of the pancreas itself or by pepsin when the pancreatic material was given by stomach. This idea was first acted upon by Croftan (52), who in 1910 prepared an extract from the press juice of pig's pancreas and heated it for three hours at 80° C. Trypsin was completely inactivated. The extract was filtered, mixed with 25 per cent glycerine for preservation and was fed with some success to diabetic patients. The next year, 1911, E. L. Scott (53) undertook to eliminate the external enzymes by ligation of the ducts and degeneration of the acinous tissue in exactly the manner employed by Banting and Best. He did not succeed in occluding the ducts completely, consequently never prepared

an extract of degenerated pancreas. He sought to accomplish the same end, however, by extraction with alcohol, and when this extract proved unserviceable on account of depressor substances, he employed an acidulated aqueous medium which lowered the D:N ratio in depancreatized dogs quite significantly.

The same year Pratt and Spooner (54) fed fresh pancreas to a dog with very much reduced carbohydrate tolerance, brought about by complete isolation of the pancreas from the intestine. They succeeded in raising his tolerance by continued pancreas feeding considerably beyond the average normal level. The next advance in our knowledge of the internal function of the pancreas grew out of Bayliss and Starling's work on secretin. Knowlton and Starling (55), working in Starling's laboratory in London, found that an extract of pancreas made in acid solution after the manner of preparing secretin enabled the heart of a diabetic dog to metabolize sugar. This result was speedily confirmed by McLean and Smedley (56) at the Lister Institute. But upon attempting to repeat the observations in conjunction with Patterson (57), Staring failed and concluded that his previous experiments with Knowlton had been defective.

It was at this point that the writer's interest became aroused at Cornell Medical College. Before Knowlton and Starling published their results the idea that the duodenal lining might have something to do with the production of the internal secretion as well as with the external secretion of the pancreas suggested itself. Accordingly a combined extract of pancreas and duodenal mucosa was prepared. It stood about the laboratory for months. Finally an opportunity came to try it on a diabetic and, happily, the extract diminished his excretion of sugar. Having in mind some of the great difficulties which had been encountered by previous workers, and especially Pflüger's principle that the internal secretion should first be proved by application to the depancreatized animal, Kramer and I (58) in 1912 set to work upon the problem, employing first the method of extraction of Knowlton and Starling, which by this time had been published. One of the first experiments performed, but with an extract prepared in much stronger acid, succeeded so well that after neutralization and boiling, upon injection into the vein of a diabetic dog it caused the urine to become sugar free in a little more than two hours and to remain

so for six hours. But alas! when next day the total excretion for the entire twenty-four hours was balanced up it was found that the dog gave back all the sugar which had disappeared from the urine and it looked as if the extract only blocked the kidney outlet temporarily. It is now almost certain from Macleod's (59) results that the true explanation lay in the temporary storage of glycogen. The idea that the duodenum contributes something to the formation of the pancreatic hormone has not proved fruitful.

The experiments were continued, and with further successes, but new difficulties were encountered. Everybody at this time thought it was unphysiological to give an extract or any foreign fluid by vein unless it were made alkaline and the apparent effect on the kidney, it was feared, might have been due to unneutralized acid; hence not only was the acid employed in extraction neutralized as had been done in the first experiments, but the fluid was made distinctly alkaline with sodium carbonate. This was the fatal step, for the anti-diabetic substance was destroyed or at least obscured by using too much alkali.

This, however, was not the end of our work. Finding that alkali alone (1% sodium carbonate) would reduce the excretion of sugar, the problem was pursued as opportunity afforded for three years, and finally in 1916, after it had been demonstrated conclusively that alkali did not cause the storage of glycogen (60) or combustion of sugar, although it might improve the conditions for oxidation in the partially depancreatized animal, pancreatic extract was once more employed. This time it was shown that an acid extract made slightly alkaline and given with sugar into the stomach of a depancreatized dog did actually cause the oxidation of sugar (61).

Kleiner and Meltzer (62) meantime had shown that finely-ground suspensions of pancreatic gland in sterile water would bring about a reduction of the blood sugar in depancreatized dogs. Their preliminary results were reported while Murlin and Kramer were engaged upon the problem and one of the depancreatized animals used by the latter was given a suspension of pancreas intravenously and subcutaneously with the result that the respiratory quotient was raised some ten points. This particular experiment has only recently been published (63). Several years later in reporting their completed experiments,

Kleiner (64) erroneously quoted Murlin and Kramer as having "always used an alkaline medium." It should be made clear that Murlin and Kramer's extracts were, in the great majority of cases prepared in acid media, but were neutralized or made alkaline before administration. Furthermore, it was shown that in totally depancreatized animals the alkali alone never raised the respiratory quotient more than two or three points, whereas the combined extract (made in acid) and weak alkali (N/20 NaoH final reaction) increased the quotient several times to ten points and once eighteen points (0.87). This result obtained in exactly the same manner has recently been confirmed many times. There was also in the earlier experiments an increased heat production and prolongation of life from this treatment.

Macleod (65) and his colleagues have been in error in supposing that these results were not considered sufficiently constant or significant "to justify more intensive research with the object of securing preparations of greater potency that could be used for treatment of diabetes in man." It was with exactly this object that work was resumed at the University of Rochester a year ago last October, as soon as a new laboratory could be organized for study of all the important criteria. Work was well under way before it was known that Dr. Banting and Dr. Macleod were interested in the problem. Nothing was known of their results beyond the fact that Banting had employed ligation of the ducts and extraction of the degenerated pancreas, until Banting and Best's first paper (delayed in reaching the laboratory) came to the writer's attention in April, 1922. By this time further favorable results upon the respiratory quotient with extracts and entirely new results with perfusates of pancreas had been obtained. These facts are stated merely for the purpose of making it clear that the results up to this point obtained at Rochester were in no way dependent upon the successes at Toronto. They therefore constitute a much more significant confirmation than would otherwise be the case.

Before recapitulating what has been accomplished the past year and a half mention should be made at this point of the favorable results reported by Paulesco (66). They were distinctly encouraging. He found that the intravenous injection of a sterile extract into depancreatized dogs brought about a diminution or even a temporary suspension of the hypergly-

cæmia and of the glycosuria; also a diminution of the excessive production and excretion of urea and acetone bodies. The effect, he found, appeared immediately, reached its maximum in about two hours, and continued for twelve hours. The method of preparation employed by Paulesco has not been available to the writer.

Banting and Best's results may be summarized briefly as follows. Extract of pancreas caused to degenerate by ligation of the ducts brings about a sharp drop in the hyperglycæmia and glycosuria of depancreatized dogs. Extract of fetal pancreas does the same. These successes led to a re-examination of the methods of extraction of adult pancreas and it was found that a slight modification of Scott's method gave an extract which upon concentration produced a very powerful anti-diabetic effect, particularly after dialysis. Collip (67) improved upon the method of extraction and purification and the resulting extract in concentrated form was first used with human cases of diabetes in January, 1922. Up to February 22nd it had been tried with hopeful results in seven cases (68).

Following the joint report of Banting, Macleod and their colleagues to the Association of American Physicians (69) and to the Royal Society of Canada (68), interest in their results has become widespread. Schafer (70) in 1916 suggested the name *insuline* for the active principle of the internal secretion of the pancreas. This name (without the final "e") has been adopted by the Toronto physiologists, but they appear to have limited its use to the alcoholic extract. In addition to the demonstration of reduced hyperglycæmia and diminished glycosuria in depancreatized dogs and human cases, Macleod, Banting and their colleagues have now shown that the respiratory quotient may be raised by injections of *insulin* to a level indicating beyond a doubt the combustion of carbohydrate (68). They have also shown that *insulin* will reduce the blood sugar in normal rabbits, will counteract the effect of epinephrin, asphyxia, etc., and will increase the glycogen content of the liver and diminish the excretion of ketone bodies in depancreatized dogs (59). More recently (71) the Toronto workers have undertaken to standardize their *insulin* (which they define as a purified alcoholic extract of pancreas) by the blood sugar test on normal rabbits, while Hepburn and Latchford (72) from the same laboratory

have added the interesting information that under its influence the normal rabbit heart may be induced to increase its consumption of sugar from a normal rate of 0.87 mgm. per gram per hour to 3.06 mgm.—nearly four-fold. More detailed data regarding the antagonistic effect of *insulin* against the hyperglycæmia of piqure, epinephrin, mechanical and carbon monoxide asphyxia and ether constitute the latest of these most important contributions.

When the first authentic reports from Toronto reached the Rochester laboratory it was seen that they contained confirmation of the method of extraction employed by Murlin and Kramer in 1913-1916. The essence of this method lay in the use of acid in sufficient amount to restrain the action of trypsin. Murlin and Kramer (63) had been led to increase the strength of the acid above that used by Knowlton and Starling because of the fact that signs of the effects of active trypsin had been seen when the extracts were given subcutaneously. Our work started off in 1921 with the use of similar extracts and we had two good experiments (73) showing marked increase in the respiratory quotient before we knew anything of the Toronto results. But we were having the same difficulties from toxic effects that the Toronto workers were having, and to obviate these we were trying the perfusion method introduced by Clark (74) when the results of Banting and Best first came to our hands. Their experience stimulated us to try more prolonged extraction and to adopt an acid (76) instead of an alkaline (75) reaction in the perfusion fluid. We soon found that we could obtain highly potent preparations by either method and that they could be administered after careful neutralization to depancreatized dogs subcutaneously, intravenously or intraperitoneally without toxic effects. Dogs rendered totally diabetic by extirpation of the pancreas under treatment, even with unconcentrated extracts, immediately exhibited improvement in all the cardinal symptoms. The blood sugar could be brought down precipitately to normal or below, the urine could be rendered sugar-free, and the respiratory quotient could be raised to 0.90 or higher by means of one or two doses. Comparison (73) was made between this aqueous method of extraction and that published by Collip in May, 1922, and it was found that with equivalent concentration the simple aqueous extraction gave results just as favorable

as the alcoholic extraction *with the advantage that toxic effects* (on dogs) *were not so frequent.* On July 17, 1922, the extract was first administered to human subjects by duodenal tube. One case (77) in particular which is shown in the chart, exhibited marked improvement as regards blood and urinary findings from this method of administration. But upon resorting to subcutaneous administration of more concentrated and more highly purified extracts the improvement was still more rapid. A number of other patients have been given the extract subcutaneously and at the time of writing there have been for several months no unfavorable effects, while the cardinal symptoms have been almost wholly eliminated. The smallest effective dose thus far (i. e., the most potent extract) was 0.5 cc. More recently even more concentrated extracts have been prepared.

Potent extracts of dog's and cat's pancreas had been prepared by perfusion (75) of a faintly alkaline Locke's solution through the pancreatico-duodenal artery. But the potency was increased when the 0.2% sodium bicarbonate was replaced with 0.2% HCl. Even without concentration these perfusates contain a sufficient quantity of the anti-diabetic substance to reduce the blood sugar, stop the excretion of sugar through the urine, and raise the respiratory quotient when given subcutaneously to depancreatized dogs in doses of 25 cc. In purified form they have also proved very potent with human cases.

The perfusion method has two advantages over any extraction method yet tried by us: (1) it yields a fluid containing considerably more of the anti-diabetic substance per unit weight of pancreas; and (2) this fluid contains relatively little extraneous protein. A method of percolation recently worked out at Rochester accomplishes the same result as perfusion but at a more rapid rate. All extracts contain a substance which will raise the blood sugar of normal rabbits or depancreatized dogs and unless this substance is removed one does not obtain the full potency of the extract. Only once out of 40 perfusions of cat, dog, pig and ox pancreas have we encountered this property in the perfusate.

Recent experiments show that the anti-diabetic substance can be precipitated (78) by means of trichloracetic acid, or acetone, or by pure ethyl, propyl, butyl and amyl alcohols, or can be salted out by means of ammonium sulphate or sodium

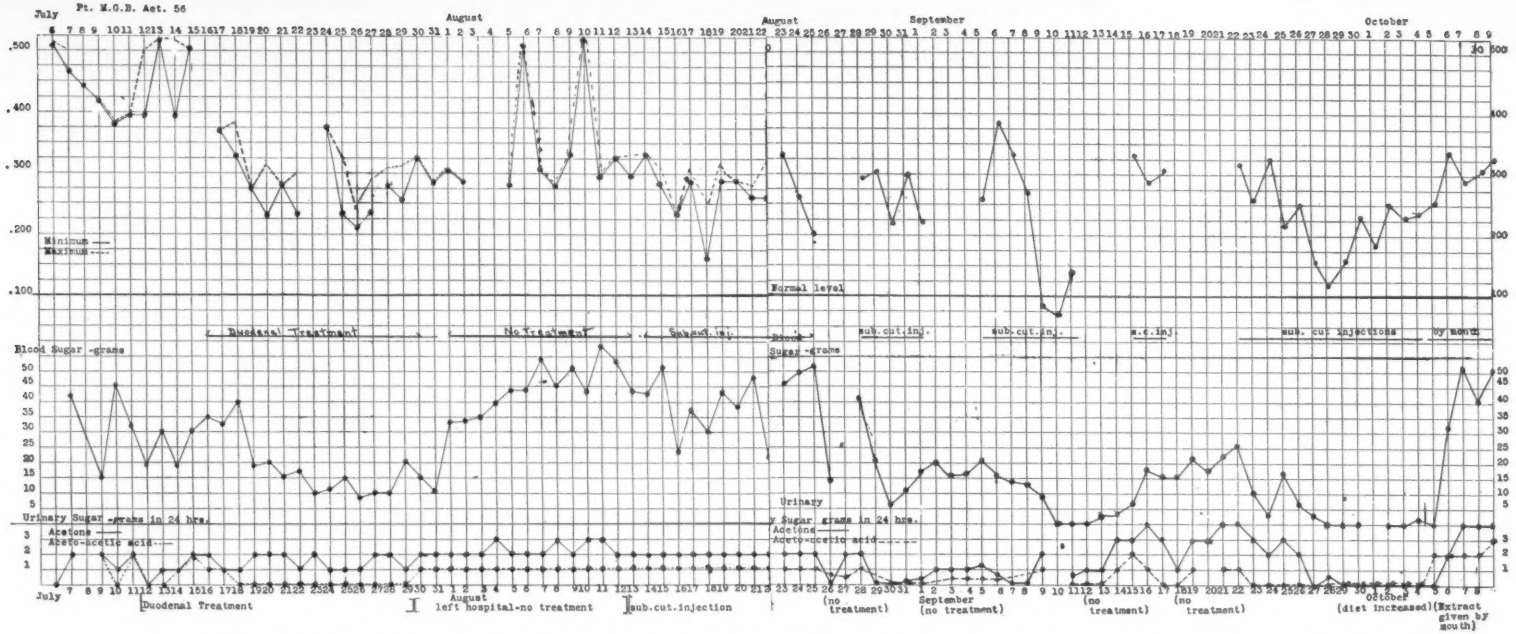

Chart showing variations in blood sugar and urinary sugar together with acetone and diacetic acid in an advanced case of diabetes mellitus treated successively first by duodenal administration of pancreatic extract, later by subcutaneous injection and finally administration by mouth. The double curve in the upper part of the chart represents maxima (dotted line) and minima (continuous line) for the blood sugar.

chloride. It is resistent to heat up to boiling temperature (79); it does not dialyze rapidly and therefore can be freed of salts, and it remains potent in slightly acid medium for at least four months. Both the solubility and stability are exceedingly sensitive to the H-ion concentration. We do not believe the potent substance is a protein; for we get potency in the complete absence of the biuret and other protein reactions and in some instances the potency seems to be in inverse proportion to the nitrogen content.

ADDENDUM

At the time of reading galley proof (June 18) further improvements (80) in the preparation of insulin had been made. These include in particular: the quantitative precipitation of the active substance from the first filtrate (after extraction in acid aqueous medium and neutralization of the excess acid) by means of sodium chloride; the removal of salt and protein by successive fractional distillation from alcohol and re-solution of the dry residue in alcohol; and final precipitation of the active substance as a powder insoluble in distilled water by simple adjustment of the reaction.

The active substance is available for oral administration in the form of a bouillon at the stage of the first filtrate or in the form of a powder which can be incorporated in tablets or capsules at the stages of precipitation with salt, or finally, in pure condition for subcutaneous administration. The effective minimal dose for oral administration as a bouillon is approximately ten times the effective minimal dose (in rabbit units) for subcutaneous administration.

BIBLIOGRAPHY

1. Minkowski & v. Mehring: Centralbl. f. klin. Med., 1889, **10**, 393; Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1890, **26**, 371-389.
2. Banting & Best: J. Lab. & Clin. M. (St. Louis), 1922, **7**, 251; Ibid., **7**, 464.
3. Minkowski, O.: Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1892, **31**, 85-189.
4. Caparelli: Biol. Zentralbl., 1892, **12**, 606.
5. Ballastini: Therap. Monatsh. (Berl.), 1893 (Oct.).
6. Ralfe: Report of the London Hospital, Clin. J., 1893 (Aug. 10).
7. Sibley, W. K.: Brit. M. J. (Lond.), 1893, 579.
8. Wood, N.: Brit. M. J. (Lond.), 1893, 64.
9. Mackenzie, H. W. G.: Brit. M. J. (Lond.), 1893, 63.
10. White, W. H.: Brit. M. J. (Lond.), 1893, 452.
11. Ausset: Semaine méd. (Par.), 1895, 376.
12. Borman: Meditzina (Russian), 1895, 195; trans. in German, Wien. med. Bl., 1895, No. 42.
13. Vanni & Burzagli: Morgagni, 1895 (July).

14. Lisser: Therap. Monatsh. (Berl.), 1896 (Feb.).
15. Spillman: Semaine méd. (Par.), 1896, 338.
16. Thesen: Deutsche Med.-Ztg., 1897, 63.
17. Lauritzen: Deutsche Med.-Ztg., 1897, 63.
18. Hougounenq & Doyon: Arch. de Physiol., 1897, 834.
19. Hédon, E.: Diabète pancreatique. Trav. de Physiol., 1898, 148.
20. Blumenthal: Ztschr. f. diätet. u. physik. Therap. (Leipz.), 1898, 276.
21. Lépine, R.: Rev. de méd. (Par.), 1900.
22. Biedl & Offer: Wien. klin. Wchnschr., 1907, **20**, 1530-1532.
23. Williamson, R. T.: Practitioner (Lond.), 1901, 417.
24. Meyer, E.: Ztschr. f. exper. Path. u. Therap. (Berl.), 1906, **3**, 58.
25. Wegele, C.: Fortschr. d. Med., 1902, **20**, 313.
26. Rennie, J.: J. Anat. & Physiol. (Lond.), 1902-3, **37**, 375.
27. Rennie & Frazer: Biochem. J., 1907, **2**, 7.
28. Cohnheim, O.: Ztschr. f. physiol. Chem. (Berl. & Leipz.), 1903, **39**, 336.
29. Hall, G. W.: Am. J. Physiol. (Balt.), 1907, **18**, 283.
30. Levene & Meyer: J. Biol. Chem. (Balt.), 1911, **9**, 97.
31. Laguesse, E. G.: Compt. rend. Soc. de biol. (Par.), 1893, **44**.
32. Vassale, Reggio Emilia, 1889.
33. Schultz, W.: Arch. f. mikr. Anat. (Bonn), 1900, **56**, 491.
34. Ssobolew, L. W.: Centralbl. f. allg. Path. u. path. Anat., 1900, **11**, 202.
35. Sauerbeck, M.: Ergebn. d. allg. Path. u. path. Anat. [etc.] (Wiesb.), 1904, 538.
36. Tiberti, N.: Arch. ital. d. biol., 1902, **38**, 253; Ibid, 1909, **51**, 117.
37. Kirkbride, M. B.: J. exper. M. (Balt.), 1912, **15**, 101.
38. Kamimura, N.: Mitth. a. d. med. Fak. d. k.-jap. Univ., 1917, **17**, 95.
39. Opie, E. L.: Disease of the pancreas; its cause and nature. Phila., 1910.
40. Herzog, M.: Beitr. z. chem. Phys. u. Path. (Brnschwg.), 1902, **2**, 102.
41. Weichselbaum & Stangl: Wien. klin. Wchnschr., 1910, **23**, 968; Ibid., 1902, **15**, 969.
42. Gutman, C.: Virchow's Arch. f. path. Anat. [etc.] (Berl.), 1903, **172**, 493.
43. Cecil, R. L.: J. exper. M. (Balt.), 1909, **11**, 266; Ibid., 1911, **13**, 595.
44. Allen, F. M.: J. Metab. Research (Morristown), 1922, **1**, 5.
45. Zuelzer, G.: Ztschr. f. exper. Path. u. Therap. (Berl.), 1908-9, **5**, 307.
46. Zuelzer, G., Dohrn, M. & Maixer, A.: Deutsche med. Wchnschr. (Berl.), 1908, **34**, 1380-1385.
47. Forschback, J.: Deutsche med. Wchnschr. (Berl.), 1909, **35**, 2053.
48. Sandmeyer, W.: Ztschr. f. Biol. (München u. Leipz.), 1895, **31**, 12.
49. Pariset: Compt. rend. Soc. de biol. (Par.), 1906, **60**, 64-66.
50. Leschke, E.: Arch. f. Anat. (Leipz.), 1910, 401.
51. Allen, F. M.: Glycosuria and diabetes. Boston, 1913, 819.
52. Croftan, W. M.: Dublin. J. M. & S., 1910, **129**, 332-336.
53. Scott, E. L.: Am. J. Physiol. (Balt.), 1911-12, **29**, 306-310.
54. Pratt, J. H. & Spooner, L. H.: Arch. Int. Med. (Chicago), 1911, **7**, 665.
55. Knowlton & Starling: J. Physiol., 1912-3, **45**, 146.
56. McLean & Smedley: J. Physiol., 1913, **47**, 137.
57. Patterson & Starling: J. Physiol., 1913, **47**, 137.
58. Murlin & Kramer: J. Biol. Chem. (Balt.), 1913, **15**, 365.
59. Banting, Best, Collip, Maclead & Noble: Tr. Roy. Soc. Canada (Ottawa), 1922, **16** (May).
60. Kramer, Marker & Murlin: J. Biol. Chem. (Balt.), 1916, **27**, 499-515.
61. Murlin & Kramer: J. Biol. Chem. (Balt.), 1916, **27**, 517-538.
62. Kleiner & Meltzer: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1914-15, **12**, 58.
63. Murlin, Kramer & Sweet: J. Metab. Research (Morristown), 1922, **2**, 19-27.
64. Kleiner, I.: J. Biol. Chem. (Balt.), 1919, **40**, 153.
65. Macleod, J. J. R.: Canad. M. Ass. J. (Toronto), 1922, **12** (June).
66. Paulesco, N. C.: Arch. internat. de physiol. (Par.), 1921, **15**, 85-109. Physiol. Abst., 1922, **6**, 580. Compt. rend. Soc. de biol. (Par.), 1921, **85**, 555.
67. Collip, J. B.: Tr. Roy. Soc. Canada (Ottawa), 1922, **16** (May).
68. Banting, Best, Collip, Campbell & Fletcher: Canad. M. Ass. J., 1922, **12**, 71.
69. Macleod, Banting, Best, Collip, Campbell, Fletcher & Noble: Proc. Ass. Am. Physicians; J. Am. M. Ass. (Chicago), 1922, **79**, 71.
70. Schafer, E. A.: The endocrine organs. 1916, 125.
71. Banting, Best, Collip, Macleod & Noble: Am. J. Physiol. (Balt.),

1922, **62**, 162-176.
72. Hepburn & Larchford: Ibid., 177.
73. Murlin, Clough, Gibbs & Stokes: J. Biol. Chem. (Balt.), 1923, **56**, 253.
74. Clark, A. H.: J. Exper. M. (Balt.), 1916, **24**, 621.
75. Clough, Stokes, Gibbs, Stone & Murlin: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 66-67; also, Murlin, Clough & Stokes: Am. J. Physiol. (Balt.), 1923, **64**, 330-347.
76. Murlin, Clough, Gibbs & Stone: Am. J. Physiol. (Balt.), 1923, **64**, 348-363.
77. Sutter & Murlin: Proc. Soc. Exper. M. (Balt.), 1922, **20**, 68-69.
78. Kimball, Allen and Piper: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, 414-416.
79. Piper, Mattill & Murlin: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, 413-414.
80. Allen, Piper, Kimball & Murlin: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, May.

CLASSIFICATION AND TREATMENT OF HYPOPHYSEAL DISORDERS*

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Experimental evidence, including injection experimentation, extirpation, etc., has given remarkably contradictory effects. Some workers ascribe certain functions to one lobe, and others the same function to a different lobe; and still others ascribe all resultant disturbance to perihypophyseal injury, or to the stalk alone. Out of this heterogeneous mass of contradictory evidence have come many classifications. The most notable classification is that of Cushing (1), which describes all conditions of perverted pituitary function as dyspituitarism, subdivided into five groups:

Group I. Cases of dyspituitarism in which not only the signs indicating distortion of neighboring structures, but also the symptoms betraying the effects of altered glaudular activity, are prominent;

Group II. Cases in which the neighborhood manifestations are pronounced, but the glandular symptoms are absent or inconspicuous;

Group III. Cases in which neighborhood manifestations are absent or inconspicuous, though glandular symptoms are pronounced and unmistakable;

Group IV. Cases in which obvious distant cerebral lesions are accompanied by symptomatic indications of secondary pituitary involvement;

Group V. Cases with a polyglandular syndrome in which the functional disturbances on the part of the hypophysis are merely one, and not a predominant feature of a general involvement of the ductless glands.

"Under each of the first four groups, there will naturally occur three subdivisions: namely (1) the cases in which the clinical manifestations of past or of existing hyperpituitarism predominate (more particularly overgrowth, resulting in gigantism when the process antedates ossification of the epiphyses—typus Launois; resulting in acromegaly when it is of later occurrence—typus Marie); (2) those in which the clinical manifestations of hypopituitarism predominate (adiposity, with a persistence of both skeletal and sexual infantilism when the process originates in childhood—typus Froehlich); adiposity with sexual infantilism of the reversive form when it originates in the adult—the type we have explained on experimental grounds and of which clinical illustrations are to be given); and (3) the mixed or transition cases exhibiting some features of both states —in other words, with evident dyspituitarism."

Bell (2) states: "From a scientific point of view, as well as for the sake of lucidity, it appears to me better to consider

*Read in abstract before the Association for the Study of Internal Secretions, St. Louis, May 22, 1922.

pituitary lesions as primary, and as secondary to disease in the neighborhood, to general disorders or to derangements of the other organs of internal secretion; and, also, in each case according to whether there is a condition of excess of secretion or deficiency—so far, at any rate, as our knowledge will allow such an estimation."

Timme (3) suggests as the best classification for purposes of therapy, one based upon a primary division depending upon the characteristics of the sella turcica, with secondary qualifications in each division, based upon the symptomatology. Our main objection to this classification would be the fact that such a large percentage of cases showing gross evidence of pituitary disturbance, show no changes in the sella turcica.

In an attempt at still greater lucidity, and feeling that the consensus of experimental, pathological, and clinical evidence justifies the conclusions at least tentatively, Engelbach and the author have devised a classification embodying the supposed functions of the individual lobes (4), (5). The clinical material, including a study from every possible angle, the response to therapy, etc., consisted at the time of the original classification of 892 endocrine cases, of which 147 were diagnosed as disorders of the pituitary gland; 350, of the thyroid; 194, of the gonads; 186, pluriglandular disorders; 10, diseases of the adrenals; and 5, thymus diseases. Of the 123 hypopituitary cases, 23 were grouped as anterior lobe; 3, as posterior lobe; and 86, as bilobar insufficiencies. The hyperpituitarisms totaled 24, of which 6 were anterior lobe; 2, posterior lobe; and 16, bilobar varieties. There were 11 cases of diabetes insipidus, some of which were associated with clinical signs of anterior lobe and posterior lobe symptoms. Pituitarism as a part of a pluriglandular complex (not included in the 147 primary pituitary disorders) occurred in 122, making a total of 269 cases in which clinical manifestations of pituitarism were present. At the present time, this material has been markedly increased, the total number of cases studied to date being 1995.

At the present time, although realizing the tentative character of the classification, the essentially questionable hypothesis, and the fact that changes necessarily will be made, we feel that we do not care to modify it. In this classification the hypophysis is considered as consisting of two lobes, the anterior and the pos-

TABLE I

HORMONIC SIGNS OF THE ANTERIOR LOBE OF THE HYPOPHYSIS

	HYPOPITUITARISM		HYPERPITUITARISM	
	Preadolescent	Postadolescent	Preadolescent	Postadolescent
A. Osseous	**A. Undergrowth. All Bones** LORAIN-LEVI type	**A. Undergrowth. Short and flat bones** only. (Normal long bones)	**A. Overgrowth of all bones**	**A. Overgrowth. Acral, short and flat bones** only. (Long bones short) **Acromegaly**
1. Stature	1. Short	1. Tall, or normal	Normal giant Eunochoid giant Acromegalic giant — **Gigantism**	
a. Measurements	a. Torso greater than lower. Span less than height	a. Varies. Torso greater than lower or less than lower (eunuchoid)	1. Abnormally tall a. Normal giant: torso=lower, span=height Eunuchoid giant: torso less than lower, span greater than height Acromegalic giant: torso greater than lower, span less than height	1. Short and stocky, or normal a. Acromegaly: torso greater than lower, span less than height
2. Head	2. Small	2. Small	2. Large	2. Large
a. Sinuses	a. Small	a. Small	a. Large	a. Large
b. Nose	b. Pointed, straight	b. Pointed, straight	b. Pointed, normal (eunuchoid giant) Blunt (acromegalic giant)	b. Blunt, rounded
c. Superior Maxilla	c. Normal	c. Normal	c. Normal, except prominent in acromegalic giant	c. Prominent
d. Chin	d. Pointed, sharp	d. Pointed, sharp	d. Pointed, except prognathism in acromegalic giant	d. Rounded, blunt. Prognathism
e. Sella Turcica (X-ray)	e. Small, except **neoplastic** type enlarged	e. Small. except **neoplastic** type enlarged	e. Normal, except **neoplastic** type enlarged	e. Normal, except **neoplastic** type enlarged
3. Hands	3. Type "en petit," one-third smaller than normal	3. Small	3. Type "en longe," one-third larger than normal. No disproportion	3. Type "en large," spade hand, wrist wide, fingers broad and clubbed. Infiltration of soft tissues over bones. Hands and head involved
a. Phalanges (X-ray)	a. Narrow, tapering, tuberosities and tufting absent	a. Narrow, tapering tuberosities and tufting absent	a. Wide, dense, tuberosities large, terminal tufting, exosteses	a. Wide, dense, tuberosities large, terminal tufting, exostoses
4. Pelvis	4. Broad, feminine type	4. Broad, feminine type	4. Narrow, masculine type	4. Narrow, masculine type
a. Genu	a. Valgum	a. Valgum	a. Varum	a. Varum

B. Genital	B.	B.	B.	B.
1. Gonads (ovary or testicle)	1. Infantile	1. Normal	1. Large, well developed	1. Large, well developed
2. Uterus	2. Infantile	2. Normal	2. Normal	2. Normal
3. Menses	3. Amenorrhea, metrorrhagia, and dysmenorrhea	3. Tendency to dysmenorrhsa, amenorrhea, and metrorrhagia	3. Normal	3. Normal
4. Sterility and Impotence	4. Present	4. Present	4. Absent (present in a few years with transition to hypoactivity)	4. Absent (present after many years with transition to hypoactivity)
5. **Secondary Sex Characters**	5. Absent	5. Present	5. Present (even after hypoactivity occurs)	5. Present (even after hypoactivity occurrs)
C. **Muscular**	C. Proportionate to development	C. Normal	C. Normal, or overdeveloped	C. Overdeveloped
1. Muscle Tonus	1. Normal	1. Fatigability frequent	1. Loss after few years' overactivity)	1. Retained after age of 40-45
D. **Mental**	D. Usually deficient or retarded	D. Average	D. Apathetic (after activity changes)	D. Abnormally developed, temperamental, loquacious, unstable
E. **Dermal**				
a. Teeth	a. Upper incisors enlarged, lateral occlusion good	a. Occasional separation and frequent enlargement of upper incisors	a. Enlarged and separated upper incisors. Lowers separated in acromegalic giant	a Separation of upper incisors constantly; frequently of lower, with prognathism
b. Hair Distribution	b. Absent	b. Normal	b. Increase on torso	b. Marked increase on extremities and chest
F. **Temperature**	F. Subnormal	F. Subnormal	F. Normal	F. Normal
G. **Pulse**	G. Slow	G. Slow	G. Normal	G. Normal
H. **Blood-pressure**	H. Hypotension, or normal	H. Hypotension, or normal	H. Normal. Hypotension after change to hypoactivity	H. Normal, or above normal

terior, with the pars intermedia as a part of the latter. The functions of the individual lobes, acting through their secretory hormones, have been considered as follows: (1) the anterior lobe regulates and controls (a) the skeletal growth and (b) the function and development of the gonads and the secondary sex characters; (2) the posterior lobe is concerned with (a) the regulation of the carbohydrate metabolism (glycosuria, hyperglycemia, sugar tolerance, and obesity), (b) the contraction of the involuntary unstriped muscles (persistalis and uterine contraction), (c) the renal secretions (polyuria), (d) the blood pressure, and (e) the body temperature. There are unquestionably many other minor functions of these lobes which are too indefinite to serve as valuable clinical evidence of activity. Reciprocal relationships undoubtedly will enter, but if present to a decided degree, usually can be recognized by their individual clinical manifestations. The syndromes, exclusive of pituitary neighborhood signs and symptoms, formerly termed glandular symptoms, are designated *hormonic* signs and symptoms, a qualification applying to all endocrine disorders. These hormonic signs and symptoms are defined as physical or metabolic changes, associated with other endocrine symptoms, due to an abnormal secretion of a ductless gland. Those pertaining to pituitary disorder are divided into physical, metabolic, and other endocrine symptoms. The physical hormonic signs are subdivided into regional and general. The general and regional signs can best be appreciated from the appended tables.

The neighborhood signs and symptoms, while important as diagnostic evidence of the neoplastic varieties and disorders, were of little value in differentiating varieties and types for the purpose of classification for diagnosis; and pituitary tumors were found associated with all types of clinical disorder, and, on the other hand, all clinical types were seen without evidence of tumor. Cushing (1) and Timme (3) both call attention to the not infrequent occurrence of a normal sella in pituitary disease. Furthermore, the incidence of pituitary tumor was so rare (about 6 per cent), that this symptomatology was practically useless as a basis for general classification; and up to the present, the histopathology of the pituitary in the absence of tumor is so meager and poorly defined that it is not dependable as a basis for classification, although we feel that the future will offer

TABLE II

HORMONIC SIGNS OF THE POSTERIOR LOBE OF THE HYPOPHYSIS

	HYPOPITUITARISM	HYPERPITUITARISM
I. **Metabolism**	I.	I.
a. Basal Metabolism	a. Decreased	a. Increased
b. Carbohydrate Tolerance	b. Increased	b. Decreased
c. Glycosuria and Hyperglycemia	c. Absent	c. Present
II. **Adiposity**	II. Marked girdle, mons and mammary	II. Absent, usually emaciation
III. **Polyuria**	III. Present (Pars Intermedia?)	III. Absent (or present with glycosuria)
IV. **Involuntary Muscle Contraction**	IV.	IV.
a. Intestinal	a. Absent; frequent intestinal atony	a. Present; frequent intestinal spasticity
b. Uterine	b. Absent	b. Present
V. **Endocrine Secretion**	V.	V.
a. Thyroid	a. Hypoactivity (hibernation)	a. Hyperactivity
b. Adrenals	b. Insufficiency?	b. Hyperactivity
c. Gonads	c. Hypoactivity (with Anterior Lobe disorder)	c. Hyperactivity (with Anterior Lobe disorder)
d. Pancreas	d. Normal (increased sugar tolerance)	d. Hypoactivity (decreased sugar tolerance)
VI. **Nervous**	VI. Apathy; Somnolence frequent	VI. Psychic instability
VII. **Temperature**	VII. Subnormal	VII. Normal
VIII. **Pulse**	VIII. Slow	VIII. Rapid

something more definite along this line. The unimportance of actual tumefaction in pituitary disease may be appreciated when we consider the fact that we recognize clinically hyperthyroidism in the absence of an enlarged thyroid, and that the degree of thyrotoxicosis is not proportionate to the size of the gland.

In the classification, the age of occurrence, which essentially modifies the picture, and the presence or absence of tumefaction have been differentiated. Of fundamental consideration have been the hormonic signs of lobar activity, considering the lobes either singly or dually, in hyper- or hypo-activity, and in hetero-activity (that is, hyper-activity of one portion and hypo-activity of another).

TABLE III

CLASSIFICATION—DISORDERS OF THE PITUITARY GLAND

I. Anterior Lobe	
A. **Hypo**activity	
1. **Pre**adolescent a. A-neoplastic b. Neoplastic	**Lorain-Levi Type**
2. **Post**adolescent a. A-neoplastic b. Neoplastic	**Amenorrhea, Dysmenorrhea, Metrorrhagia** reacting to Anterior Lobe treatment. No signs of Posterior Lobe disorder
B. **Hyper**activity	
1. **Pre**adolescent a. A-neoplastic b. Neoplastic	**Gigantism** (no signs of Posterior Lobe disorder)
2. **Post**adolescent a. A-neoplastic b. Neoplastic	**Acromegaly** (no signs of Posterior Lobe disorder)
II. Posterior Lobe*	
A. **Hypo**activity	
1. Pars Intermedia (?)	**Polyuria** (Bab) (Reaction to Pituitrin. Signs of Anterior Lobe and Pars Nervosa disorder absent)
2. Pars Nervosa	Pituitary **Obesity** (Decreased metabolism, increased sugar tolerance. Polyuria and signs of Anterior Lobe disorder absent)
B. **Hyper**activity	Hypophyseal **Glycosuria** (Increased metabolism, decreased sugar tolerance. Polyuria and signs of Anterior Lobe disorder absent)
III. Bilobar*	
A. Anterior and Posterior Lobes	
a. **Hypo**activity	**Froelich's Type** without, or with polyuria (Biedl)
b. **Hyper**activity	**Gigantism** or **Acromegaly** with **increased** metabolism and **decreased** sugar tolerance. Adiposity absent
c. **Hetero**activity	
1. Anterior Lobe hyperactive Posterior Lobe hyperactive	**Gigantism** or **Acromegaly** with **Polyuria**
2. Anterior Lobe hypoactive Posterior Lobe hyperactive	**Genital Aplasia, Nanism, Amenorrhea,** etc., with **Pituitary Glycosuria** (Increased metabolism; decreased sugar tolerance)

*(1)Pre- and (2) Post-adolescent varieties and (a) A-neoplastic and (b) Neoplastic types are subdivisions under each activity (Hypo- and Hyper-) as given under I, Anterior Lobe.

From this formulation of a temporary classification based upon what we believe to be a judicious selection of experimental evidence, we naturally proceed to a consideration of therapy. Therapeutic endeavor must not be haphazard, but rather directed along definite lines, such as those that a classification offers; and the clinical observation of therapeutic results along such lines will materially aid in the verification or negation of such a classification.

There has been much argument concerning the relative values of uniglandular and pluriglandular therapy. Upon the

basis of a cell selectivity, pluriglandular therapy has been advocated, and it is probably true that the body cell has to a degree the power of selecting from the blood stream certain of those elements essential to its maintenance. But the power or rejection is probably not of a corresponding degree of efficiency, as is well exemplified in the untoward effect produced by feeding thyroid or thyroid combinations to a patient whose thyroid function is normal or excessive. Again, from the standpoint of experimentation and rational advance in clincial observation, the author has felt that uniglandular therapy is the method of choice, realizing that pluriglandular syndromes may and do commonly exist requiring a combined therapy. This combined therapy, however, is based upon the clinical observation of the hormonic signs representing the endocrine deficiency of two or more glands, and more valuable evidence may be acquired if first one gland is sufficiently tried and the clinical effects accurately noted, then the other, and then the combination of the two or more endocrine substances, corresponding to existing deficiencies.

As regards the standardization of pituitary material, we have little satisfactory information. There is no certainty that, even though the internal secretion exists in relatively large quantities in the fresh gland, it persists in the desiccated or chemically treated product. To use the fresh gland, of course, is not usually feasible, and uncertainty will exist until the active principle is isolated, synthesized, and accurately standardized. Considering the wide variability in the commercial products, a valuable point might be interpolated, and that is that the clinical observer should adopt a single preparation, and upon its effects base his therapeutic conclusions, for the present at least.

Another difficulty in the human being is the determination of the proper dosage. Anterior lobe has been prescribed by different workers in doses from 1 grain three times a day to 100 grains three times a day, with very little clinical evidence to guide the therapeutist; although the author considers that even small doses (for instance, 5 grains three times a day) have in a number of cases definitely intensified the headache associated with hyperpituitarism. As regards posterior lobe extracts, particularly when hypodermically administered, Engelbach and the author have suggested the "intestinal reaction" as a guide to

physiological tolerance (4). This intestinal reaction consists of a cramping, colicky sensation in the abdomen, succeeded within a few minutes by bowel evacuation, usually occurring five to fifteen minutes after the injection. The amount of pituitary extract (for example, pituitrin) required to produce this reaction varies widely in different individuals. At one time it was thought that in hypopituitarism the amount required to produce reaction might be considered as an index to the degree of deficiency, although clinical observation never fully verified this hypothesis. It may be said, however, that in many cases of frank hypopituitarism, it has required two or three times the dose of pituitrin to produce this reaction than in the normal individual. In regard to the oral administration of the posterior lobe substance, there is little to guide the clinician compared, for instance, to the manifold symptomatology resulting from the overadministration of thyroid extract. The intestinal reaction described as a result of the hypodermic injection of pituitrin has never been observed following the administration of the pituitary substance by mouth, nor have the vascular and general reactions. (Fully described in the reference above.)

Another source of general difficulty, particularly in the appreciation of therapeutic effects, is the great number of isolated clinical conditions that have been described as reacting or non-reacting to pituitary therapy, without the correlation of these symptoms with other pituitary signs or conforming them to definite classification. Among these conditions are tumor, headache, obesity, epilepsy, dysmenorrhea, amenorrhea, nervous and mental states, hibernation, diabetes insipidus, diabetes mellitus, adiposis dolorosa, shock, urinary incontinence, alopecia, onychauxis, ileus paralyticus, uterine inertia, decreased libido, sexual impotency, arterial hypotension, hyperthyroidism, asthma, orthodontial anomalies, and a variety of other conditions.

TUMOR

First, as regards tumor, especially when associated with hyperpituitarism, particularly acromegaly, the literature abounds with many successful procedures, including both the x-ray and radium.

X-ray and radium treatment. Schaefer (6) reports 8 cases of tumor of the hypophysis with acromegaly treated by this means, and accentuates the fact that the head should be so placed that the hypophysis is situated in the focus of the rays. Webster (7) reports a case of early acromegaly in which sixteen treatments were given with hard filtered rays through the temporal and frontotemporal areas, with good results. The first eleven were given at weekly intervals, then they were given fortnightly, and latterly at monthly and longer periods. The headaches were relieved, the "queer" feelings disappeared, the irritability and depression disappeared, and the optic discs returned to normal, while the fields for vision, especially for red, became greatly enlarged. Jaugeas (8) was successful in the use of x-ray treatments in tumors and hyperactivities of the hypophysis, stating that the change in the visual fields parallels the benefit and forms a gauge to the efficacy of treatment. Cavazzini-Bergamo (9) reports two cases of hypophyseal tumor with acromegaly which were greatly benefited by x-ray treatment by the Béclère method—deep radiotherapy through the two temporal and frontal regions, at first every week, later less frequently.

Gramenga (10) treated a case by x-ray directly from the palate for an hour twice a month. The subject was forty-five years of age and had had amenorrhea for thirteen years. After eight treatments, the headache disappeared and the ophthalmoscopic signs became normal. The symptomatology returned later, however, and did not respond to treatment. Béclère (11) reports a case of a giantess, aged sixteen; operation had been proposed for severe headache and visual trouble, but radiation weekly for ten weeks from the frontotemporal areas gave total relief from headache and improved the field of vision in the right eye in two months. Williams (12) reports a case of a woman, aged thirty-seven, with severe headache, nausea, dizziness, and vomiting, two months' diplopia, slight haziness of the optic papilla, and arteries which were very small. The headaches disappeared, and there was general improvement. Terrien (13) reports similar results. Favorable results of x-ray radiation in similar cases are reported by Kupperle (14), Gunsett (15), Cauvin (16), Calamet (17), and de Lapersonne and Cantonnet (18). Quick (19) reports three cases of *radium emanation.* In the first subject he imbedded five fine glass capillary tubes of radium emanation (unfiltered and a total strength of 15 millicuries) through trocar needles in the lower portion of the tumor and left them there. He attributes improvement in the headache, vertigo, and vision to the radiation, although some benefits may have been secured from previous operations, one the removal of an adenoma a year before, and a second for recurrence a month previous to emanation. Later, one tube of emanation, a total of 30 millicuries, filtered by 0.2 millimeter of aluminum and enclosed in a small rubber tube, was inserted in the space where the floor of the sella was removed and left for an hour and thirty minutes. A month later, two fine capillary tubes of emanation, a total of 3.2 millicuries, were imbedded through trocar needles in the same manner as the first treatment. At the time of writing, the condition had been definitely improved. The second patient, a woman of thirty-seven, during a pregnancy at the age of thirty, began to have attacks of vertigo, severe and persistent headache, impaired vision, and a cessation of menstrual function three years after the first symptoms were noted. Since the cessation of menstruation, there had been a persistent lactation. Gigantism and fat deposits were extreme. The sugar tolerance was very much increased. Under local anesthesia, a submucous resection of the nasal septum, back to the sphenoid, was done. The sphenoidal sinuses were opened, but the floor of the sella was not removed. A 0.2 millimeter aluminum tube,

containing 40 millicuries of radium emanation, encased in rubber, was introduced into the sinus, placed against the floor of the sella, and retained in position by gauze packing for twelve hours. After this there was definite relief of pressure symptoms, but the headaches again became more severe, although the vision continued to improve and the vertigo disappeared. About eight months later, 605 millicuries of radium emanation, filtered by 2 millimeters of lead and 0.5 millimeter of silver, were placed over the right temporal region, at a distance of 4 centimeters from the skin, left in place for five hours, and repeated the following day over the left temporal region. After this there was a lessening of the headache, but it did not disappear. The vision improved appreciably and lactation ceased. The third subject died of meningitis a month following treatment, so that no report was possible.

Bertolotti reports a number of cases treated by x-ray and radium, with notable improvement in several. He feels that the best results are obtained in early cases. Ranschburg (20) reports two cases of dystrophia adiposogenitalis with tumor treated by x-ray, the first subject presenting headache, fainting giddiness, loss of vision, increasing papillitis, and weakness. The skull was divided into eight sections and treated with Roentgen ray. In the course of four weeks, eight treatments of thirty to forty minutes each were given, followed by twenty minutes of treatment through the hard palate. At the end of six months, the symptoms of tumor, except those due to destruction, had disappeared, while, in spite of treatment with organ extracts, there had been no change in the signs of dysfunction caused by the probable total destruction of the hypophysis. The second subject, a young woman at the age of twenty-one, weighed between 80 and 90 kgm., increasing within a few years to as much as 115. There was an abnormally large and deep sella turcica; tumor was suspected. After ten days of Roentgen ray treatment the patient was able to distinguish light from darkness. A short time later, the vision increased to about half normal, and the facial paralysis was cured. There was no effect upon the impairment of smell and taste, nor upon the growth of hair.

Ascoli and Faginoli (21) suggest an interesting phase of the subject, namely, the stimulation of a deficient pituitary by means of deep radiation with the x-ray, whereas all previous attempts have been directed to the destruction of tissue. The first case was one of dystrophia adiposogenitalis, without demonstrable tumor; the subject had received several months' pituitrin and endospermin treatment, with but slight improvement. He had four radiations of the hypophysis at intervals of one month. At each sitting, three different fields were radiated, one frontal and two temporal, for thirty-six minutes in all, at a distance of 45 cm., using an aluminum filter of 2 mm., S. Et. 18-20 cm. and M. A., 3.5. Twenty-five days after the first irradiation, pubic hair began to grow, the penis and testes increased in size, erections became frequent and complete, and there was increased sexual tendency. The height increased 5 cm., and the fat tended to diminish, the chest measurement dropping from 86 to 81 cm. The second, a patient with scleroderma who had not responded to other treatment, received radiations over both the hypophysis and the thyroid, with signs of some improvement. Other cases showed failures or varying degrees of improvement. Fraenkel (22) also expresses a belief that the stimulating action of slight irradation may prove successful in endocrine function.

Surgical treatment. Concerning the surgical treatment of pituitary tumors, little need be said. Quick (19) in his review of the literature, emphasizes the wide variation in operative mortality and

the relatively small group of cases in which surgery offers anything worth while. Kanavel (23) places the operative mortality in the neighborhood of 35 per cent in the hands of those doing little cranial surgery, but mentions the work of Hirsch (24) and Cushing, where the rate is down near 10 per cent. In his own series of 15 cases, there were 4 deaths. Cushing (1) reports of 43 cases, a total of 61 operations, 10 per cent. (The technique is now probably improved.) Moritz (25) states that the visual disturbance and headaches are relieved by surgery, while the metabolic and trophic changes may be altered but slightly, or not at all. A consideration of the various operative procedures and the relative merits of the same cannot be considered in this article.

HEADACHE

Pardee (26), from a review of the literature and a consideration of 7 cases, concludes that pituitary disturbance constitutes a fairly common cause of headache, usually located between the temples, deep in behind the eyes, and associated with dyspituitary signs. He believes that the sella turcica in most cases shows demonstrable abnormalities. In a large percentage of these cases, the headaches and accompanying symptoms disappeared upon the administration of the whole pituitary gland substance, in doses from .25 grain to 2 grains three times a day. He also accentuates the fact that these headaches may be physiological, occurring during the menses and pregnancy.

Blumgarten (27) states that pituitary headaches are distinctive, that the patients all show characteristic markings, such as a broad forehead, with prominent supraorbital regions, overlapping teeth, changes in the secondary sex characteristics, amenorrhea, impotency, sterility, or a pituitary psychology (e. g., males having feminine psychology). The basis for the treatment of the headache, he feels, is the fact that physiological hypertrophy of the pituitary gland in a small sella turcica is the cause, and that injection or feeding of pituitary extract removes the need for hypertrophy. Blumgarten found no success with placenta and corpus luteum in many subjects whose headaches yielded to pituitary extract.

Timme (3) calls attention to the association of migraine with other signs of pituitary disturbance, particularly the association with the menses, believing that at this time the pituitary body enlarges. He feels that the sella turcica of a person subjected to these disturbing factors is too small to accommodate the enlarging gland, and pressure against the surrounding structure of the hypophysis occurs, producing first erosion of the sella, and then pressure against the softer structures beyond, such pressure occasioning headache. He narrates post-mortem confirmation of unilateral pressure exerted by an enlarged hypophysis upon the cavernous sinus, in a case of migraine, by Deyl, at Paris; the work was later confirmed by Plavec. He also feels that the phenomenon of epilepsy may be upon a similar basis, a periodic enlargement of the hypophysis in a sella not sufficiently large to accommodate it, causing the critical moment, thus precipitating an attack, and from this standpoint attaches some importance to the frequently recognized association of epilepsy and migraine.

Glassburg (28) presents a case of pituitarism in which the bitemporal headache, muscular fatigue, etc., were probably relieved by pituitary extract, 4 to 8 grains a day by mouth. Cushing (1) felt that the headaches associated with pituitarism, usually bitemporal, often severe and persistent when there is considerable glandular hypertrophy, are presumably due to the distention of the glandular

envelope, and noted that they often subsided, and coincidentally presumably, with a stationary process or with a full distention of the dural capsule and widening of the sella. He felt that splitting of the tense capsule of the gland in two cases produced relief.

Engelbach and Tierney (4) used the term *pituitary headache* as not referring to the type of headache caused by neoplasm of the pituitary or other brain tumor, for the reason that the headache is found present in many cases free from evidence of enlargement of the sella turcica or other signs of intracranial pressure. Its frequent occurrence in diseases of the pituitary is sufficient reason for the term, and will stimulate closer observation of hormonic signs and symptoms in every case of persistent recurring headache, particularly those which are associated with menstrual disturbance. The association of migraine with general pituitary signs, its association with the menses, its frequent cessation at the menopause, and the fact that in the author's experience many cases of migraine have been definitely benefited by pituitary therapy, suggest the more than casual relationship between the complex migraine and pituitary disturbance.

OBESITY

The author has felt that the characteristic obesity of hypopituitarism represents deficiency of the posterior lobe, although Beck (29) believes that the development of obesity is due to an anterior lobe deficiency, and has found definite changes in the deposition of obesity under anterior pituitary lobe therapy (2.5 grains two or three times a day) and thyroid from 0.5 to 1 grain two or three times a day. The author feels that the loss of weight is not an adequate criterion for the effect of treatment, but that the redistribution of fat and reductions in the characteristic areas of increase are of more significance. Unfortunately, in these cases no adequate conclusion can be drawn, because of the fact that thyroid was used in conjunction with the anterior lobe pituitary substance.

Von Dziembowski (30), in a case of dystrophia adiposogenitalis, examined microscopically a small piece of the biceps. The picture showed a few muscular fibers, and these atrophic, with an enormous increase of fatty tissue. In this case, treatment with thyroid, adrenal, and testicle was unsuccessful; but injections of an ampule of hypophysin were tried, with splendid success. The patient lost weight, libido returned, and the muscles became thinned, with an increased tonus. Most of the author's cases have been combinations of genital hypoplasia and obesity of the ordinary Froehlich type; or that occurring after adolescence, consisting of obesity of the characteristic type and genital disturbance, as manifested by amenorrhea, loss of libido sexualis, etc. These cases have been treated largely by a combination of both the anterior and the posterior lobe substances by mouth, and antuitrin and pituitrin hypodermically injected, some showing definite response, as will be noted in type cases. In other cases, thyroid has been combined; and a *most important* point must be here accentuated, that is, that cases have been seen in which thyroid would produce response only to a certain degree. When this was stopped, and pituitary substance substituted, response might

be again noted to a certain degree; but the optimum response in many of these cases, and the response much greater than that secured by either thyroid or pituitary substance alone, was secured by the combination of these two substances. Timme has called attention to the fact that very small doses of thyroid (1/100 or 1/10 grain every day, or on alternate days) will frequently enhance the effect of pituitary administration.

EPILEPSY

Lowenstein (31) reports 16 cases of epilepsy studied from the standpoint of possible endocrine disturbance, particularly hypophyseal. Five cases, or 31 per cent, showed one or more features possibly to be ascribed to pituitary change. In 8 cases, or 50 per cent, roentgenographic examination showed changes in the sella. In this series, 5 cases were apparently benefited by pituitary gland administration, the preferable product seeming to be extract of the whole gland, and the most satisfactory method of treatment, hypodermic injections. No improvement was shown in cases showing typical epileptic constitution, nor in cases with abnormalities of the fundi or visual fields. Other physical signs referable to the hypophysis, such as sella turcica changes, and variations in weight or height, offered no criteria to judge success or failure.

Engelbach and Tierney (4) report 6 cases of epilepsy associated with definite signs of pituitary deficiency: 4 male, 3 of which appeared to be pure anterior lobe insufficiency, and 1 bilobar; 2 female, both of which showed hormonic signs of insufficiency of both lobes. Three cases were under observation for a considerable period of time, 2 showing definite benefit from pituitary treatment. The other 3 subjects were not under observation for a sufficient length of time to appreciate clinical results. Numerous other isolated cases have been reported in the literature, many with apparently successful response. Tucker (32), in a study of 200 subjects, 63 (or 31.5 per cent) of whom revealed some evidence of pituitary disturbance, feels that there is a definite relation between the undersecretion of the pituitary gland and a group of periodic convulsive attacks, usually termed epilepsy, but that this group is divided into a chronic hypopituitary type and a transitional hypopituitary type, by both clinical and roentgenographic evidence; pituitary gland feeding has a markedly beneficial effect, not infrequently leading to cure.

NERVOUS AND MENTAL STATES

Many peculiar nervous and mental phenomena have been described as associated with pituitary disturbance. Fliess (33) describes a complex nearly always observed in women after pregnancy, or in women with diseases of the ovaries, consisting of obstinate neuralgias (sciatica, occipital neuralgia), extreme weariness, psychic disturbances (diminished concentration of thought), polydipsia, polyuria, and enuresis, reacting favorably to pituitary preparations. Weygandt (34) feels that two psychic symptoms have not been fully appreciated in association with hypophyseal obesity: (1) feeble-mindedness, and (2) a cheerful disposition, with psychomotor unrest. The findings are not uniform, but reveal certain general factors, especially feeble-mindedness of more or less severe grade up to the severest dementia of idiocy, frequently in combination with a cheerful, amiable disposition and a tendency to joking and harmless, irritable, restless behavior. There are also individual patients with more than average intelligence and earnest, almost depressive habitus. The author accentuates the first type, although our experience cer-

tainly has shown the preponderance of the group showing an intelligence either normal or above normal, with the earnest and at times depressive habitus. Tucker (32) described a number of pituitary psychoses peculiar to adolescence, separating them into four groups, giving the roentgenographic findings of the sella turcica and the psychoses associated with both the hyper- and the hypo-active types. He concludes that in these various psychoses of pituitary origin, in many cases showing decreased pituitary secretion, the response to pituitary feeding was prompt and satisfactory.

The author has noted as a most constant association with pituitary disease, a marked mental disturbance. The main features have been nervous instability, irritability, failure of concentration, dissociation of ideas, memory defects, inconstancy, temperamentalism, occasional brainstorms, emotionalism, wanderlust, and a variety of other psychic manifestations. Physical complaints have shown frequent paresthesias, varying from tingling to definite formication. These symptoms frequently respond early to proper substitutional therapy—long before there are definite responses in the objective sphere.

GLYCOSURIA

Although the pancreas has received fundamental consideration in the etiology of diabetes mellitus, there are many authors who feel that other endocrine organs, such as the adrenals, thyroid, or hypophysis, may be factors in the production of glycosuria. Borchardt (35) found that injections of the whole gland caused glycosuria in rabbits. Franchini (36) could not confirm this, although Cushing (1) reported similar results. The association of acromegaly with glycosuria has been frequently noted in the literature (Borchardt, Falta (37), Schlesinger (38), Cushing (1), Frankl-Hochwart (39), and others), and there are a number of reports of acromegalic and diabetic subjects dying in coma. Many have felt that the association of diabetes with pituitary disease was due to secondary disease in the pancreas, which contention apparently has been verified by some observers, but careful post-mortem examination in other cases of acromegaly and diabetes showed no pathological change whatsoever in the pancreas. Koopman (40) reports two cases of diabetes mellitus apparently definitely benefited by the administration of hypophysis tablets, and cites another case reported by Steensma (41) of a young girl showing some tendency to adiposity, with an enlarged sella turcica and glycosuria, who responded successfully to hypophysis substance. Koopman draws the conclusion that, although he is aware that proof is lacking that these cases are hypophyseal diabetes, from the therapeutic results it is probable that the hypophysis had played an important part.

Engelbach and the author, in a series of 711 pituitary cases (including pluriglandular disorders with pituitary involvement), found 8 cases of glycosuria, 3 of which have been reported in Tice's Practice of Medicine. All of these cases except one failed to respond to pituitary therapy, although it is felt theoreitcally

that those cases associated with hyperpituitarism, such as acromegaly, should be definitely treated along such lines as x-ray or radium directed to the pituitary. Glycosuria has been frequently noted early in the case of acromegaly, later disappearing. This disappearance may coincide with the transition of hyper- to hypo-activity, which so frequently occurs, and should be, as in other cases of hypopituitarism, an indication of intensive pituitary therapy, both by feeding and hypodermic administration.

DIABETES INSIPIDUS

There is an extensive literature concerning the rôle of the hypophysis in the production of diabetes insipidus. Earlier workers [Talqvist (42), Meyer (43), Seiler (44), Socin (45)] thought the condition due to lack of the kidneys to secrete concentrated urine. Finkelnberg (46), Schwenkenbecher (47), Falta (37), and Forschbach and Weber (48) did not believe that the concentrating power of the kidney was lost, but that there was a pathological stimulation which produced larger amounts. Spaether (49) considered diabetes insipidus to be a paresis of the renal vasomotor nerves, of either central or peripheral origin, and Ebstein (50) believed that the condition was due to a primary polydipsia, with a resultant polyuria. Bernard (51), in 1849, proved that by puncturing the medulla oblongata and the brain stem in various places, definite poluria would occur. In 1870, Eckhard (52), produced polyuria by various types of irritation of the vermiform process of the middle lobe, and injury to the posterior lobe of the brain. Kahler (53), in 1886, produced permanent polyuria and polydipsia in animals by injecting small quantities of concentrated silver nitrate solution into various portions of the brain.

The hypophysis began to receive attention after Schafer demonstrated that the administration of posterior lobe extract produced polyuria. This work was confirmed by Schafer and Oliver (54), Magnus and Schafer (55), and Schafer and Herring (56). Later, Pentimalli and Quercia (57), van den Velden (58), and Motzfeldt (59) found divergent results. The previous theories of hypersecretion of the pituitary as a factor in poyluria, began to swing toward the theory of hyposecretion. Bab (60) believed diabetes insipidus to be due to hypofunction of the pars intermedia, or a disturbance of the reception of the secretion in the pars posterior, or a propagation of the secretion in the cerebral lecunae. Biedl (61) noticed many clinical discrepancies, such as the association of diabetes insipidus with dystrophia adiposogenitalis. The same association has been noted by Fearnsides (62), Marañón and Pintos (63), and Schuenemann (64). The pathology in the literature is full of contradictory results. Houssay (65), believes it to be due to injury to the neighborhood tissue; Leschke (66), to lesions in the midbrain, especially the tuber cinereum. Claude and Lhermitte (67), and Olaechea (68) have reported cases in which only the infundibulum was involved. Most of the literature, however, is concerned with the response of the syndrome to the administration of the posterior lobe extract, and many striking results are recorded. Of course, it must be remembered, as has been frequently stated, that the results from the admin-

istration of the posterior lobe extracts do not positively prove the pituitary origin of diabetes insipidus, but they certainly are suggestive.

Engelbach and the author have observed 15 cases, 11 of which were reported in 1920 (4). Of these, 5 had no definite osseous, adipose, or general changes, or other hormonic signs that would relate them specifically to pituitary disorder. On the other hand, 6 had very striking pituitary signs other than polyuria and nervous manifestations. In 5 of these subjects, posterior lobe extract (pituitrin) exerted a decided influence upon the polyuria and other symptomatology. In 4 cases, including 2 tumors, pituitrin was not instituted. In 1 case, showing what we deemed to be an associated disorder of the anterior lobe, tending to gigantism, there was absolutely no response to pituitrin treatment. Another case, however, of similar makeup, did respond. In all cases it was necessary to continue the treatment indefinitely, and in only one case, after the condition had been controlled by subcutaneous treatment, was the patient able to continue on pituitary treatment by mouth (in the dosage of 10 grains three times a day), without a return of the symptomatology. However, if the oral administration was discontinued, there was a prompt return of the polyuria.

Most cases reported in the literature have failed to respond to the oral administration, although a few isolated cases have been observed responding to pituitary substance which had been salol-coated, possibly preventing some destructive chemical transformation in the stomach. Rees and Olmsted (69) were able to control a case of diabetes insipidus as effectively with salol-coated capsules of the desiccated posterior lobe, as with hypodermic extract.

In the author's recent series of cases, there has been one of more than passing attention, and that is the association of marked diabetes insipidus with sphenoidal sinusitis. At the present time, the sphenoidal condition has been practically cleared, but the polyuria persists, requiring 2 cc. of pituitrin (0) daily for control.

SMOOTH MUSCLE TONE

The use of pituitrin in many conditions with a fundamental loss of smooth muscle tone, has been successful. Mikhailoff (70) reports the successful use of pituitrin in the treatment of urinary incontinence, reporting 19 cases, all successfully treated, and stating that

four injections are sufficient to cure the condition. Bandler (71) accentuates the value of pituitrin in post-operative tympanites, and in the stimulation of intestinal peristalsis. Its clinical value in paralytic ileus is well known, and its successful use in uterine inertia and in obstetrics is so well accepted that comment is unnecessary, except to mention the apparently growing objection of many obstetricians to its routine use.

SEX DISORDERS

Hoffstätter (72) reports good results from the administration of pituitary preparations in cases of amenorrhea accompanied by uterine and ovarian hypoplasia. The author has found amenorrhea rather constantly associated with deficiency of the anterior lobe, associated with infantilism and genital hypoplasia in the preadolescent deficiency, and amenorrhea, with decreased libido sexualis, in the post-adolescent deficiency of the anterior lobe. In some of these patients there was definite response to anterior lobe substitution alone, whereas in others absolutely no response was shown. Dysmenorrhea and menorrhagia are more questionable in their association with pure pituitary disease; although clinical responses in our own hands to this line of therapy have warranted more prolonged and careful clinical investigation along this line, with particular attention to the association of these symptoms with other pituitary signs, and to conformity of the afflicted individuals to definite types, as suggested in our classification. Concerning the psychological phase, such as frigidity, decreased libido, and impotency, there is no question about the frequent association with pituitary deficiency, and experience has shown numerous responses of these particular conditions to pituitary substance administered hypodermically and by mouth, especially the anterior lobe preparations. In certain cases, types of which will be shown, there has been a definite stimulation of the genitalia, including marked growth of the testes and penis, attributed to anterior lobe substitution alone.

BLOOD PRESSURE

The association of endocrine dyscrasia with hypertension has received considerable attention; Engelbach's (5) analysis of 500 endocrine cases showed that 46, or 10 per cent, had a blood pressure above 160, all cases in which a diagnosis of nephritis or alteriosclerosis was suspected having been excluded. Of these, 30 per cent showed pluriglandular deficiency, and it was impossible to determine the dominating influence. A combination of pituitary and thyroid deficiency was exhibited by 26 per cent; 25 per cent were associated with the menopause; 11 per cent showed hormonic evidence of only pure pituitary disturbance, 4 with deficiency, and 1 with hypersecretion. This association is of interest, especially considering the fact that, contrary to the bulk of animal experimentation, our experience has shown that almost 50 per cent of the subjects show an immediate and direct depressor action following the subcutaneous injection of 15 minims of pituitrin (0), this reduction in blood pressure varying from 10 to 30 mm. of mercury.

GLAND THERAPY

The treatment of other endocrine diseases based upon reciprocal relationship has received considerable attention, particularly hyperthyroidism. Hoffstätter (72) found marked improve-

ment in 15 cases of Basedow's disease following repeated injections of 1 cc. of posterior lobe extract, followed for a time by the oral administration of desiccated pituitary substance. He concludes that the anatomical changes in the thyroid after hypophyseal therapy indicate an influence of the thyroid, in the sense of an inhibition of secretion with respect to the pituitary. Many other observers have reported varying effects. The author's experience has been decidedly unsatisfactory.

A variety of other conditions have been reported as associated with pituitary disturbance, and variable results recorded. Eye conditions have been especially prominent, particularly the response of various hemianopsias, retinitis pigmentosa, etc. In general, it may be deduced, from a review of the tremendous literature that has accumulated, that the pituitary plays a rôle in many of the above conditions, and that the recorded responses to substitutional therapy cannot be dismissed as purely coincidental; although one must appreciate the tremendous value of experimental physiology in placing the entire subject upon a sound basis and realizing that experimentation to date offers a variety of conflicting evidence. It must be remembered that laboratory subjects, from tadpoles to dogs, are essentially different from the genus homo, and that from careful, well controlled, correlated clinical observation, our most valuable, pertinent, and applicable information is to be secured. One cannot help noting that in the literature generally an isolated syndrome is selected and discussed, particularly with regard to therapeutic response, without suitable correlation with other hormonic signs, both physical and mental, or with chemical and metabolic observations. For this reason, it is difficult to draw conclusions, either favorable or unfavorable. This lack of correlation and conformity leads us to accentuate the value of a classification, based upon what appears to be the most acceptable experimental and clinical evidence, as a means of furthering our investigations along definite lines and enabling us to evaluate more correctly therapeutic response. We may eventually come to feel that the pituitary is a glandular entity, with no particular distinction to be made between its component lobes (as Bell is inclined to believe); but we feel that investigation along the lines of separated function will enable us more quickly to reach that conclusion, provided it be the true one. Or, on the other hand, if

the gland is physiologically dualistic, investigation along the lines of such a classification will enable us more quickly to confirm or to reject.

Another point that has not been sufficiently emphasized, and which should have particular appeal to the pediatrician, is the early recognition and treatment of pituitary disorders. Harvey (73) called attention to the desirability of early diagnosis of endocrine deficiency, and the greater amenability to treatment in that stage. Our experience has fully verified and accentuates this point. Our most decided therapeutic results (for instance, in pituitary obesity) have occurred in the earlier years of life. The earlier the disorder has been recognized and treatment instituted, the more effective and decided has been the reaction. In those cases in which it has been possible to institute treatment a few months after the disorder became evident, remarkable responses were achieved.

Another and most perplexing consideration, taking into account the tremendous number of possible combinations, is the reciprocal involvement of other glands. Because of this intricate reciprocal relationship, there has been given full play of diagnostic fancy in the realm of pluriglandular syndromes. We feel that each gland has a definite system of characteristic hormonic effects and signs, and with proper clinical investigation of the many pluriglandular syndromes, the glands affected may be determined, and frequently the gland which is physiologically preponderating. There is no doubt that theoretically there are probably always minor reciprocal effects in all endocrine disturbances, but practically we believe that we see uniglandular syndromes, e. g., frank hyper- or hypo-thyroidism, presenting characteristic and distinctive symptoms. Another point for consideration is the probability that one gland is fundamentally at fault and others show a secondary disturbance, and that therapy directed to the primary glandular imbalance may automatically correct the reciprocal involvement. We have also found that many of the pituitary insufficiencies have been in their earlier stages apparently uniglandular, and that after a variable length of time, usually a year, there almost constantly occurs a secondary reciprocal involvement of the thyroid or of the gonads. We have found also that, after this reciprocal involvement, the diagnosis of which is based upon the associated hormonic signs, there

is less likelihood of successful response to therapy, either singly or combined. We have found the most constant reciprocal relationship to be a combined deficiency of the pituitary and the thyroid, and that, whereas these subjects will respond to a degree to thyroid therapy alone or to pituitary therapy alone, the optimum response is invariably secured by a combination of the two.

Another point that needs definite accentuation, and one insisted upon particularly by Pottenger (74), is the remarkable association of endocrine disturbance with the sympathetic nervous system; and to this secondary sympathetic nervous system response, we must look for the explanation of many of our clinical symptoms, vasomotor responses, muscular phenomena, reflex changes, etc.

It is deemed advisable to demonstrate a few cases exemplifying what we feel to be the salient features of the classification, followed by a number of cases showing hormonic responses to therapy.

CASE I. MISS M. L., GEN. NO. 727, AGED 18, CLERK*

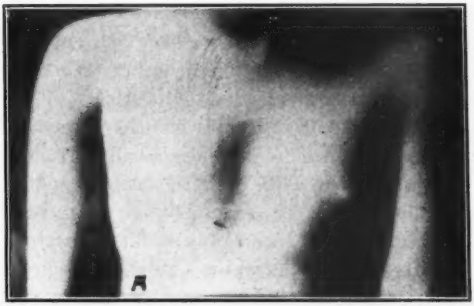
Chief complaints. The patient complained of amenorrhea (having had no period at the age of 21 years). Weight at birth was normal. The first tooth erupted at six months, and all deciduous teeth were present at the end of the second year. The patient walked not later than the thirteenth month, and was talking well at the age of one and one-half years. Mentality during childhood and early adolescence was rather above normal. No adiposity or localized puffiness of the hands, feet, etc., was noted at any time. No changes occurred in the skin or appendages (including perspiration). There have been no particular gastrointestinal or nervous disturbances. No development of primary or secondary sex characters has occurred, and no increase in growth since the age of thirteen or fourteen.

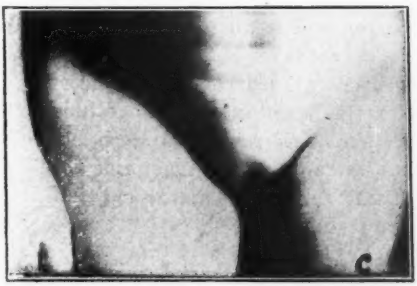
Past history. The patient had had measles, possible typhoid at the age of fourteen and frequent tonsillitis, followed by otitis media. There was nothing noteworthy in her *personal* and *family history.*

Physical examination. The patient was 78 lbs. in weight and 4 ft. 4 in. (132 cm.) in height. From vertex to symphysis she measured 27 in. (68.25 cm.); from symphysis to soles of feet, 25 in. (63.25 cm.). The span was 56 in. (142 cm.). The hand, "en petite," was of typical hypopituitary type (one-third smaller than normal), without clubbing or tapering of fingers. The head was rather large in proportion to the rest of the body; it was 20½ in. (52 cm.) in circumference; the superior maxilla measured 16¼ in. (41 cm.); the inferior maxilla at the tip of chin, 15¼ in. (39 cm.). The circumference at the navel was 25 in. (63.25 cm.); at the hips, midway between trochanters, 29¼ in. (74 cm.); at the middle of the thigh, 13¾ in. (34.75 cm.); and of the leg, 10 in. (25.25 cm.). There was complete absence of secondary sex characters, very slight lanugo on the mons veneris, absolutely no hair in the axillæ or on the face. The breasts were not

*Reported in full in Med. Clin. N. Am., St. Louis number, Nov., 1920 (Endocrine Amenorrhea, Wm. Engelbach.)

developed. The face was typically infantile. The hairline was rather low, the eyebrows very thin; the nose was slightly retrousse; no adiposity was present. The pulse was slow, but otherwise normal; the blood pressure was 124/90. The profile showed slight recession of the chin; the mouth showed recession of the lower jaw, with poor occulsion of the anterior teeth; the *upper incisors were very large, lateral canines very small;* all permanent teeth were present except the posterior molars. Both lobes and isthmus of the thyroid were slightly full.





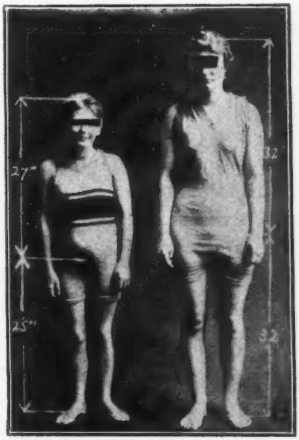


Fig. 1. (A) Note the infantile, virgin type of breast development. (B) Case 1, age 19. Note the general infantilism, feeles, and underdevelopment of the osseous system compared with the normal girl of corresponding age. (C) Infantile vulva; absence of secondary sex characters.

The *urine* was negative, except for a slight trace of albumin. The *blood*, including Wassermann test, was normal. *Carbohydrate tolerance* was increased; blood sugar the first hour tested 0.180%; the second hour, 0.120%. The *basal metabolism* was 0.108%.

Radioscopy showed a normal sella turcica, and epiphyseal lines clearly evident in the head of the radius and in all metacarpals and phalanges. Complete ossification had taken place in carpal bones; the phalanges were free from tufting or mushrooming; the bones were slender.

The above case is believed to correspond to the Lorain-Levi type of hypopituitarism, and, according to our classification, represents a pure anterior lobe deficiency of the preadolescent type, evidencing marked osseous underdevelopment and a decided genital hypoplasia, with amenorrhea. The patient was first seen in 1919 and remained intermittently under treatment for practically a year. The treatment consisted entirely of anterior lobe substitution: gland substance by mouth, 10 grains, three times a day; and "Antuitrin" hypodermically, from 5 minims to a dosage as high as 2 cc. daily. There was no response in the development of the primary or secondary sex characters, no production of menstrual periods, and only a slight increase in growth, despite the fact that skiagraphic evidence disclosed open epiphyses and suggested the possibility of growth.

A perusal of the literature and personal communication with Dr. H. Lisser, of San Francisco, who has observed and treated a number of similar cases, bring out the fact that the preadolescent type of anterior lobe hypopituitarism does not readily respond to treatment, especially when seen and treated after the condition has been long established. On the other hand, in our experience, cases of anterior lobe deficiency occurring after puberty and manifest by such symptoms as amenorrhea, loss of libido sexualis, decreased muscle tone, etc., have responded much more satisfactorily to substitutional therapy, that is, anterior lobe substance by mouth, 5 to 10 grains, three times a day, and "Antuitrin" hypodermically, 1 to 2 cc. daily.

CASE II. MISS K. S., GEN. NO. 2237, AGED 18. REFERRED BY DR. H. C. RUDDICK, EVANSVILLE, IND.

Chief complaints. The subject had complete amenorrhea. She often complained of severe, dull temporal headaches, radiating directly inward, at times associated with unconsciousness and convulsions. There had been a noticeable gain in weight (over 20 lbs. during the past three years), particularly distributed about the girdle and bust, with increased deposition in the supraclavicular areas, on the backs of the hands, and about the ankles. The hair was increased in dryness, and tended to fall out. There were no marked changes in the nails or teeth. There was increased nervousness, irritability, and fatigability. Cardiac palpitation and slight dyspnea were noted after exertion. Pigmentary changes were manifest, transient in

character and usually associated with the headaches. Constipation was complained of, and nocturnal insomnia without somnolence.

Course. The syndrome dated back to puberty. The first menstruation occurred at the age of 15, was normal and four days in duration; the second period was one month later, since which time there has been complete amenorrhea. All other complaints dated to this time. Chief among them was the headache, extremely severe, frequently requiring morphine for relief, dull, boring in character, temporal, radiating directly inward, without retro-ocular or midfrontal localization, and unilateral. At times it was associated with unconsciousness and convulsions of tetanic character. They have occurred regularly once or twice a week, for the past three years, never associated with visual disturbance, scotomata, nausea, or vomiting. Coincident with occurrence of headache, there was a gain in weight of about 20 lbs., particularly about the girdle and breasts; also increased deposition in the supraclavicular areas and on the backs of the hands, and a suggestion of cuffing about the ankles. The hair showed increased dryness and tendency to loss. There were no other dermal changes, except transient chloasma pigmentation, usually associated with headache. There has been an increase in general nervousness, irritability, apprehension and restlessness, cardiac palpitation, and constipation. There have been no polyuria, polydipsia, polyphagia, nor change in the visual field. The patient had received hypodermic injections twice weekly for a number of months (probably a corpus luteum preparation), without relief. Dilatation of the cervix and curettage were performed, and douche and tamponade treatment given, without avail. Two months preceding our observation, the patient received Burroughs, Welcome & Company's "Mixed Glands No. 2." This caused slight loss of weight, but no other change.

Past history. The patient had measles at the age of twelve *Personal* and *family history* were negative.

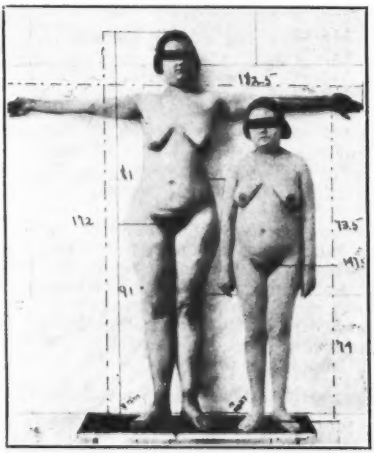


Fig. 2. Case II, age 18. Amenorrhea, associated with underdevelopment of the osseous system, representing anterior lobe deficiency. Note the suggestion of posterior lobe deficiency in the charactetristic obesity. This subject is compared with a normal girl of corresponding age.

Physical examination. The patient was abnormally small (see comparison of figure with normal). She was 112 lbs. in weight and 4 ft. 10½ in. (148.5 cm.) in height. From symphysis to soles of the feet she measured 29½ in. (74.75 cm.), and from symphysis to vertex, 29 in. (73.5 cm.). She was of a general pituitary type, with slight tendency to obesity, fullness about the lower abdomen and padding on the lateral aspects of the thighs. The skin was slightly dry. The hands were classically small, with short fingers and slight padding on the dorsa. *Head.* There was a faint brownish pigmentation about the forehead; the *ears, eyes, nose* and *mouth* were normal. The *chest, heart, abdomen, genitalia* and *reflexes* were normal also.

The *urine* was negative, except for two or three leucocytes per high power field (non-catheterized specimen). The *blood*, including Wassermann test, was normal. *Sugar tolerance.* The blood-sugar, after a fifteen-hour fast, tested 0.065%; one hour later, following 1.59 gm. dextrose per kg. of body weight, 0.112%; two hours after dextrose, 0.113%. *The basal metabolic rate* was —25%.

Pituitrin test:—

	Blood Pressure	Pulse	Temperature	Respiration
	118/70	80	98	18
9:40—Pituitrin (0) m. xv. subcutaneously.				
9:45—	118/75	82		
9:50—	120/85	80		
9:55—	115/85	82		
10:00—	118/80	80	98	20

Pallor during test, no abdominal or other disturbances.

Adrenalin test:—

	Blood Pressure	Pulse	Temperature	Respiration
	115/80	80	98	20
11:35—Adrenalin Chloride (1:1000) m. vii. subcutaneously.				
11:40—	118/75	86		
11:45—	118/80	84		
11:50—	115/80	84		
11:55—	112/75	80		
12:00—	115/75	80		
12:05—	113/70	90		
12:10—	118/75	90		
12:15—	118/75	88	98.2	18

During test, nervousness and tremor.

A *skiagram of the carpal bones* showed normal ossification; epiphyses about the wrist were not united. A *skiagram of the skull* showed a small *sella turcica*, well defined, without excavation or erosion.

Report of *ocular examination* (Dr. B. D. Ravdin, of Evansville, Indiana): No impairment of vision was observed, no intraocular nor optic nerve alterations, no scotomata, no enlargement of the blind spot of Marriott, but there was slight alteration in the visual fields for form and color, showing slight contraction of the temporal fields from above downward and slight contraction below; this was present in both eyes (however, the observer did not construe it to be a typical or true bitemporal hemianopsia).

This case exemplifies, we believe, a deficiency of the anterior pituitary lobe, manifest by underdevelopment of the skeletal system, amenorrhea, etc. The obesity occurring coincidently suggests posterior lobe involvement. The headaches are possibly pituitary, and there unquestionably is a secondary thyroid defi-

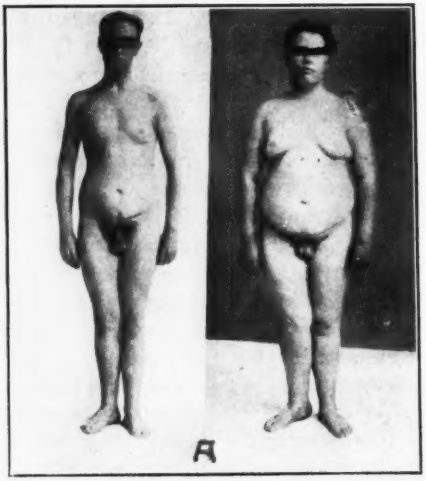
ciency, as noted in the dermal changes and the low basal metabolic rate. The following treatment was recommended: (1) anterior lobe pituitary substance, 2½ grains and pituitary substance, entire gland (Parke, Davis & Co.), 7½ grains, three times a day; (2) thyroid gland substance, beginning with ¼ grain, three times a day and increasing to tolerance; (3) "antuitrin," 1 cc. hypodermically two or three times a week; and (4) "Pituitrin (0)" hypodermically two or three times weekly, beginning with a dosage of 5 minims and increasing to tolerance; the index to tolerance was the so-called "intestinal reaction," consisting of abdominal cramping and desire for defecation, occurring fifteen or twenty minutes after the hypodermic injection. This treatment was persisted in for a period of six months, and then the patient, because of her improved condition, ceased to report to her physician. A report received a year later states that the headaches were not so severe nor so frequent, morphine having been required on but one occasion, at which time the necessity was questionable. The weight had decreased 10 lbs. *The menstrual periods had become perfectly regular,* of the twenty-eight-day type, four to five days in duration, with no pelvic pain, but usually associated with frontal headache of eight or ten hours' duration, during the first day.

CASE III. P. B. M., GEN. NO. 1438, MALE, AGED 15. REFERRED BY DR. NEIL MOORE, ST. LOUIS

History. The patient was normal at birth. Dentition occurred normally, and locomotion and speech were not remarkable. Development was normal until the age of seven, at which time, following a mild attack of measles, the patient began to gain weight rapidly, reaching 105 lbs. at the age of ten and 175 lbs. at the age of fourteen; the existing weight was 205 lbs. The increased adipose tissue was distributed particularly about the upper thighs and abdomen. The patient complained of occasional headache and of being markedly drowsy and sleepy during the day. He perspired easily, and stated that his hair grows very rapidly. Other symptoms were indefinite visual disturbance, increased thirst, without polyuria, and some tendency to constipation. The mentality was normal for the age, without tendency to decreased cerebration. Diffuse superficial tenderness existed over the entire body. *Past history.* The patient had measles at the age of seven (to which he dates the adiposity) and later, questionable malaria. The *personal history* is unimportant. *Family history.* The father is 6 ft. in height, weighing 300 lbs. The mother has a normal endocrine makeup.

Physical examination. The patient weighed 205 lbs. From symphysis to vertex he measured 33½ in. (85 cm.); from symphysis to soles of the feet, 32½ in. (82.5 cm.). The span was 66½ in. (168.5 cm.). There was very marked adiposity, more or less universal, but definitely increased about the pelvis and shoulder girdles and upper

portions of the thighs. The mammæ were overdeveloped. There was a slight amount of hair in the axillæ and over the mons and a lanugal growth on the face. The head was small. The hands were fairly well developed and normal in size. No definite pigmentation was seen. There was very marked genital aplasia, particularly of the penis:



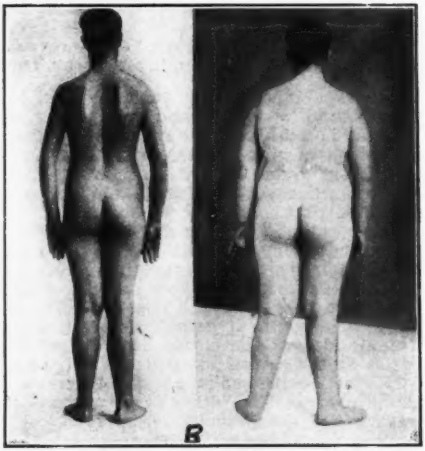


Fig. 3. (A) Case III, age 15. Note the remarkable change following treatment—definite decrease in obesity and striking change in genitalia. Despite definite contour changes, there still is suggestion of feminine type. (B) Posterior view of the same subject.

The measurements were as follows: Bust, 39½ in. (100 cm.); level of navel, 40½ in. (102.75 cm.); level of anterior, superior spine, 43½ in. (110.25 cm.); thigh, upper third, 27 in. (68.5 cm.); middle of leg, 15 in. (38 cm.). Diffuse hyperesthesia was manifest over the entire body. The pulse rate was 80; the blood pressure, 140/80. *Regional.* The frontal incisors were slightly separated. The teeth, generally, showed early decay. The thyroid was not palpable. There was a slight systolic murmur at the apex, disappearing on complete inspiration. A similar murmur, with the same characteristics was observed in the pulmonic area. Large fat folds were seen along the lateral upper aspects and lower portion of the abdomen.

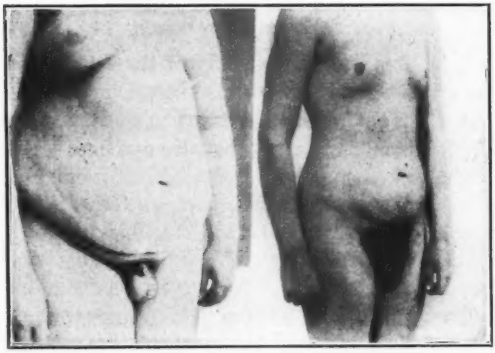


Fig. 4. Close-up of the genitalia of Case III before and after treatment. Note the striking loss of obesity about the breasts, hypogastrium, and mons, although there still is evident a remnant of hypogastric padding. Note also the increased genital development.

The *urine* was negative. The hemoglobin in the *blood* tested 95%; leucocytes, 10,500; erythrocytes, 5,420,000. Wassermann examination was negative. *Carbohydrate tolerance.* The blood-sugar, after a fifteen-hour fast, tested 0.054%; the first hour, after 1.59 gm. dextrose per kg. of body weight, 0.132%; the second hour, 0.068%. The *basal metabolism* was —18%. The *antuitrin thermic* test produced 0.2 degree rise in temperature in fifteen hours.

Radioscopy showed normal carpal, metacarpal and phalangeal bones and no tufting or mushrooming.

The patient passed from observation and was not seen again until two years later. The treatment had consisted of from four to six months' administration of the following: (1) anterior lobe pituitary substance, 2.5 grains, and pituitary substance, entire gland, 10 grains, three times a day, after meals; (2) "Antuitrin" 1 cc. hypodermically, daily; (3) "Pituitrin 0" hypodermically, daily, beginning with a dosage of 5 minims and increasing gradually to tolerance. Notation shows the remarkable loss of weight and comparative changes in measurements which may be noted from the table, complete disappearance of the somnolence, headaches, precordial pain, etc., and gradual development of libido, nocturnal pollutions, erections, and decided genital growth.

Comparative Table of Measurements

	June, 1920	April, 1922
Weight	205 lbs.	149½ lbs.
Height	5 ft. 4 in. (162.5 cm.)	
Symphysis to vertex	32½ in. (82.5 cm.)	31 in. (78.75 cm.)
Symphysis to soles of feet	31½ in. (80 cm.)	37 in. (93.75 cm.)
(Apparent discrepancy due to convexity associated with former obesity.)		
Span	66½ in. (168.5 cm.)	72 in. (182.5 cm.)
Bust	39½ in. (100 cm.)	35¼ in. (89.25 cm.)
At level of navel	40½ in. (102.75 cm.)	29 in. (73.5 cm.)
At level of anterior, superior spine	43½ in. (110.25 cm.)	34 in. (86 cm.)
Thigh, upper third	27 in. (68.5 cm.)	21¼ in. (53.75 cm.)
Middle of leg	15 in. (38 cm.)	14 in. (35.5 cm.)

As may be noted from the study of the comparative photographs, there has been a remarkable change in general makeup, marked loss of weight, with redistribution of obesity. The padding about the mammary region has disappeared, although still showing slight prominence. The padding in the epigastrium and over the mons has practically disappeared. The hips, formerly convex, now show concavity, with slight fullness about the upper thighs. The obesity, although less, is still suggestive of the former makeup. Although the makeup is more masculine, there is still a suggestion of the habitus femininus, especially in the distribution of the pubic hair. Remarkable growth in the genitalia has occurred, the present size of the penis being 7.5 cm., and the length of the testes, 5 cm.

The above case exhibits a classical preadolescent bilobar insufficiency, the anterior lobe deficiency being represented by the infantile genitalia, the posterior lobe deficiency by the adiposity. There has been a decided response following the institution of treatment, although care must be exercised not to fall into the danger of the *post hoc* argument, because of the well-known fact that similar spontaneous changes do occur without the exhibition of medication.

CASE IV. T. K., GEN. NO. 2951, MALE, AGED 12

Chief complaints. The subject complained of obesity and genital hypoplasia. There was dyspnea after moderate exertion. A tendency to hypersensitiveness, with moderate emotionalism was noted. These symptoms had been manifest for six years (dating back to the removal of the tonsils and adenoids at that time). There had been gradual gain in weight, including 30 lbs. during the last year, but no collateral history of vertigo, syncope, edema, scotomata, headache, polyuria, polydipsia, etc. The father does not believe that there has been proper genital development.

The *past history* is unimportant, except for the removal of the tonsils and adenoids, to which the symptomatology dates. It may be stated parenthetically that it has not been uncommon to find an endocrine syndrome apparently dating to this procedure. The *personal history* is negative. *Family history.* There is marked obesity on the paternal side, the father's brothers weighing from 265 to 400 lbs.; one uncle has diabetes.

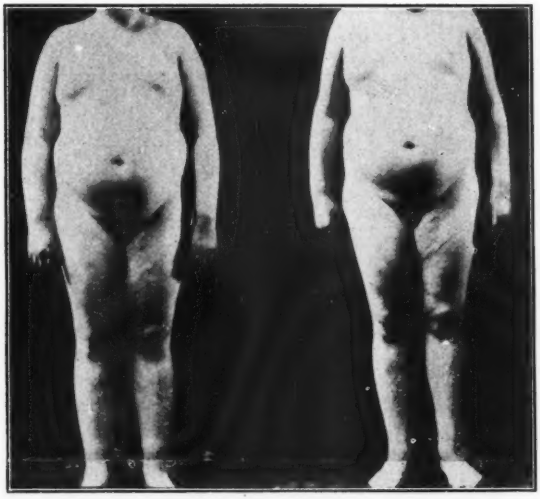


Fig. 5. Case IV, age 12. Note the redistribution of fat and the definitely increased genital development. (For comparative measurements, see text.)

Physical examination. The patient was 199 lbs. in weight and 5 ft. 6 in. (167.5 cm.) in height. Measurement from the symphysis to the soles of the feet was 35 in. (88.75 cm.); from symphysis to vertex, 31 in. (78.5 cm.). The span was 70 in. (177.5 cm.). There was definite obesity of girdle type, padding on the lateral aspects of the hips, extending down to the junctures of the middle and lower portions of the thighs, and some fullness about the hypogastrium and mons. The fingers were long and tapering, with some padding on the dorsa of the fingers and hands. Slight supraclavicular padding was seen. The skin was somewhat dry, without infiltration. The *head* was normal except for padding anterior to the ears and about the angles of the jaw. The *ears* were normal. The *eyes* were normal except for thinning of the brows at the outer halves. There was slight high saddling of the *nose.* The *mouth* and *teeth* were normal. the *neck* was short and obese. The *chest, heart, abdomen, genitalia, rectum* and *reflexes* were normal.

The *urine* was negative. The *blood,* including the Wassermann test, was normal. *Functional kidney test* showed 35% phenolsulphonephthalein in two hours. *Sugar tolerance test:* The blood sugar, after a fifteen-hour fast, tested 0.104%; one hour later, following ingestion of dextrose (1.59 gm. per kg. of body weight), 0.185%; two hours after dextrose, 0.150%. The *basal metabolic rate* was —20%.

Pituitrin test. One cc. of "Pituitrin 0" injected subcutaneousyl showed a prompt depressor effect, occurring within ten minutes and persisting for one hour, showing a drop in the systolic pressure of 20 mm., with no appreciable change in the diastolic reading except a brief initial rise. The pulse was definitely decreased—from 110 to 90. *Adrenalin (Goetsch) test:* One-fourth cc. (1:1000 solution) injected subcutaneously showed a brief and transient rise, occurring in both systolic and diastolic pressures at the end of thirty minutes, returning to normal in forty-five minutes, with no appreciable change in the pulse.

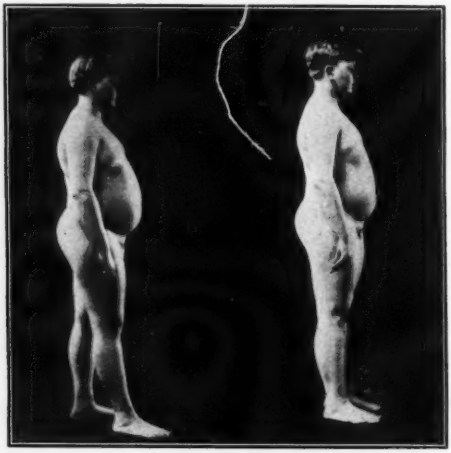


Fig. 6. Lateral view of subject, Case IV, showing definite decrease in adiposity.

Radiogram of the skull. The sella turcica in anteroposterior diameter measured 10 mm.; depth, 8 mm. Anterior and posterior clinoid processes were well visualized; there was no erosion nor excavation. *Radiogram of the hand* showed that all carpal centers were present, that there was no delay in ossification and that unguinal phalanges were tapering.

Diagnosis. The case was diagnosed as hypopituitarism, bilobar, preadolescent, associated with secondary hypothyroidism. The following treatment was instituted: (1) pituitary substance, entire gland, ½ gr. after meals; (2) "Pituitrin 0," 15 minims hypodermically, weekly. Two months following the institution of this treatment, the following notation was made: "Patient completely changed. Formerly a marked disinclination for physical work, content to sit and read by the hour; whereas now patient takes a very active interest in baseball and other sports of boyhood and has disinclination to sedentary pur-

suits. Is very much more alert, cerebration increased, with better progress in school. No decided loss in weight, but marked redistribution, decided diminution in obesity about face and neck, loss of 7 in. (17¾ cm.) about waist and 3 in. (7½ cm.) about hips. Most striking change has been definite increase in size of the genitalia, which can be appreciated from comparative photographs." Observations made four months later showed still more striking changes. The redistribution of adiposity was more definite, particularly about the hips, the lateral surfaces of which were assuming a more masculine character. The abdominal pads were decreased in size, likewise those over the mons. The genitals showed pronounced development, particularly the testes. The penis was somewhat increased in length, and the patient had definite erections. The scrotum was developing, separating from the perineum. The pubic and axillary hair had appeared since the last observation. There was desire for male companionship and boyhood sports, and alertness and capacity for leadership were strikingly increased.

CASE V. MR. G. K., GEN. NO. 1637, MALE, AGED 39*

Chief complaints. Extreme somnolence was manifest in the daytime and insomnia at night. There was enormous obesity, weight being 346 lbs. Marked thickness and harshness of the skin was noted, with padding about the neck, hands and feet. There was disturbance of speech, due to thickness of the tongue, and dribbling of saliva. Dyspnea was marked. There was diminuation of visual acuity, loss of libido and impotency. *Duration.* These symptoms had lasted for eight months. The history was elicited with great difficulty because of inability to keep the patient awake. He fell asleep while answering questions, and, when aroused, had no memory of the former interrogation. He was insensitive to ordinary stimuli, requiring hard shaking to arouse. The obesity dated to the age of fourteen, at which time he weighed 120 lbs. At the age of twenty-three he weighed 170 lbs.; at twenty-seven, 220 lbs.; and at thirty, 250 lbs. Eight months ago, weight was 291 lbs.; three months ago, 310 lbs.; at the time of examination, 346 lbs. Somnolence began eight months ago, gradually increasing in intensity, until at this time the patient was wont to go to sleep while walking, eating, or attempting conversation. The voice had become inarticulate; his speech was slurring and mumbling. The skin had become harsh, coarse, thick, and dry, comparable to leather. He perspired freely about the face and upper chest (the remainder of the body was dry). Complete loss of libido had occurred in the past three months, and visual disturbance in the past six months.

Past history. The patient had measles, mumps, chicken pox and diphtheria in childhood, and small pox, pneumonia, and pleurisy in adult life. *Personal* and *family history* are unimportant.

Physical examination. The subject was 6 ft. (182.75 cm.) in height, and 346 lbs. in weight. There was marked obesity, universal,

*Reported in full in Tice's Practice of Medicine, W. F. Prior Company, Inc., Hagerstown, Md., 1922, 8, 587. (Pituitary Hibernation or Somnolence Wm. Engelbach & J. L. Tierney.)

particularly about the lower half of the face, neck, chest, abdomen and extremities. The fingers and toes were spade-like and stubby; he wore a No. 11 shoe. There was dyspnea in the recumbent position. The skin was very thick and inelastic, and fixed to the underlying tissue. No pigmentation was observed. There was considerable abnormal distribution of hair about the chest and lower abdomen. The pulse rate was 88. Somnolence was marked. The *head* was large, of an inverted triangular shape, with rounded chin. *Regional examinations* showed no special findings of interest, other than those noted under the general.

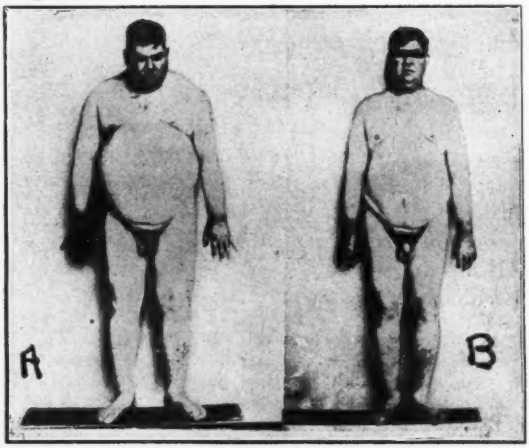


Fig. 7. (A) Note the marked obesity about the hypogastrium and mons, mammary development, spade-like hands, and stupid, apathetic expression. (B) The same case after treatment. Note the marked decrease in obesity, loss of apathy, increase in alertness, and erectness of position.

The *urine* showed traces of albumin and a few granular casts. The *feces* were normal. The *blood*, including Wassermann and differential, was normal, except for a slight increase in erythrocyte count and hemoglobin estimation. The *blood sugar*, after fasting, tested 0.052%; following the ingestion of 300 gm. dextrose and intramuscular injection of 1:1000 adrenalin, 0.088%.

Ophthalmoscopic examination. Vision in the right eye was 20/32; in the left eye, 20/32. Both external recti were faulty; the fields for form were normal; the media were clear; the optic discs were clear in outline. There was temporal pallor of both discs. The vessels, especially the veins, were engorged and tortuous. Color vision was normal.

Radioscopy showed a small sella turcica.

Diagnosis. The case was diagnosed as bilobar hypopituitarism, occurring in late adolescent life, with an undoubted secondary hypothyroidism. The general appearance of the individual would suggest early hyperactivity of the anterior lobe of the pituitary, with later transition to hypoactivity. Coincident with this anterior lobe activity, there was progressive insuffi-

ciency of the posterior lobe, and later, at the age of thirty-eight, secondary insufficiency of the thyroid. Treatment instituted was first thyroiod gland substance in dosage of 2 to 4 grains three times a day. Mentality became improved, and somnolence and nocturnal insomnia were greatly relieved by the use of thyroid alone, and the patient lost 34 lbs. during the first two weeks. After this, the weight remained stationary, and administration of large doses of thyroid produced symptoms of hyperthyroidism, requiring withdrawal of the treatment. After the maximum effect had been procured from thyroid medication given to tolerance, it was noted that further reduction in weight and improvement of other signs were accomplished by the addition of "Pituitrin 0" hypodermically, in dosage of 8 to 15 minims daily.

The patient was examined four months later, and a decided change was noted. There was a marked reduction in weight, with change of posture. The skin became loose, relaxed, and moist; the hair softer and more easily controlled. There was marked improvement in mentality. The accompanying table shows the comparative figures, and it will be noted that the most important effect was the loss of weight of 71½ lbs.; in the circumference of the hips, 15½ in. (39.25 cm.); of the chest, 6½ in. (16.5 cm.); of the neck, 2¼ in. (5.75 cm.). There was reduction of weight from 346 to 274 lbs.; and of systolic blood pressure from 158 to 135 mm.

Comparative Table of Measurements

	March 3, 1918	July 1, 1918
Weight	346 lbs.	274½ lbs.
Measurements:		
Chin	25¾ in. (65 cm.)	22 in. (56 cm.)
Neck	20½ in. (52 cm.)	18¼ in. (46 cm.)
Chest	51 in. (130 cm.)	44½ in. (113 cm.)
Navel	52½ in. (133 cm.)	46 in. (117 cm.)
Hips	59 in. (150 cm.)	43½ in. (110 cm.)
Thigh (at junction of upper and middle thirds)	21 in. (53 cm.)	21 in. (53 cm.)
Calf	15 in. (38 cm.)	14½ in. (37 cm.)
Humerus	16½ in. (42 cm.)	12¾ in. (32 cm.)
Forearm	13½ in. (34 cm.)	10¼ in. (26 cm.)
Wrist	9½ in. (24 cm.)	7¼ in. (18 cm.)

This case was reported in full in Tice's Practice of Medicine, but is herewith demonstrated to bring out the fact that, in the combined pituitary and thyroid deficiency, the optimum response is secured from a combination of these two endocrine preparations.

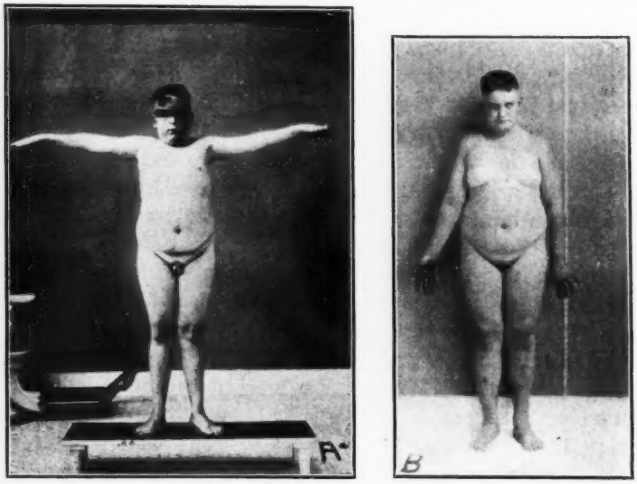


Fig. 8. (A) Case demonstrating hormonic signs of bilobar hypopituitarism. Note the characteristic girdle obesity and genital hypoplasia. (B) Bilobar hypopituitarism, demonstrating the characteristic obesity and genital hypoplasia.

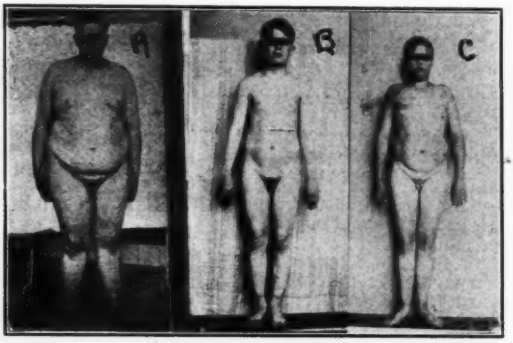


Fig. 9. Varying grades of hypopituitarism, boys of approximately the same age, all showing osseous underdevelopment and genital hypoplasia, representing anterior lobe pituitary deficiency. Case B shows slight obesity suggestive of posterior lobe deficiency. Case C shows this adiposity to a greater degree, as may be noted in the padding about the hypogastrium and mons and the feminine contour of the hips. Case A shows the combined deficiency adiposity plus genital hypoplasia, representing Froehlich's syndrome, or bilobar hypopituitarism (preadolescent).

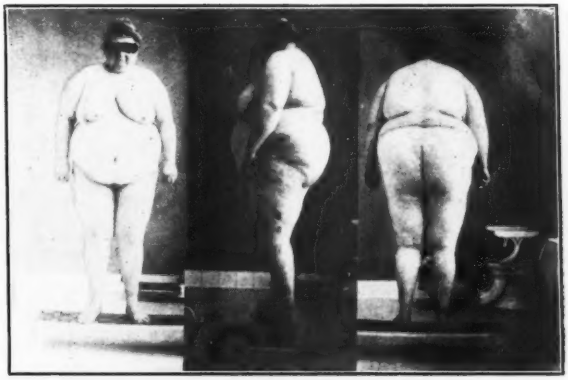


Fig. 10. Note the characteristic girdle adiposity, with fullness about the hypogastrium, mons, and hips, extending to the juncture of the lower and middle thirds of the thigh. Note the gracile character of the legs and arms, indicating the absence of a thyroid element.

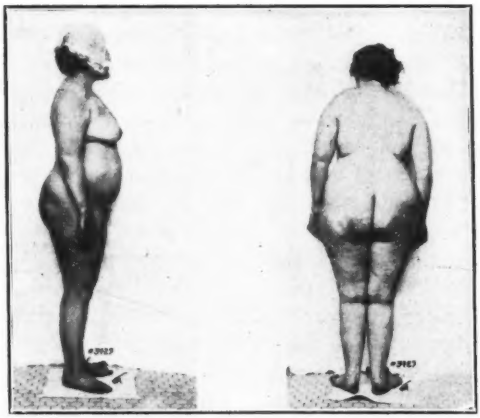


Fig. 11. Hypopituitarism, with the characteristic girdle obesity. Note the sharp delimitation at the lower portion of the thigh.

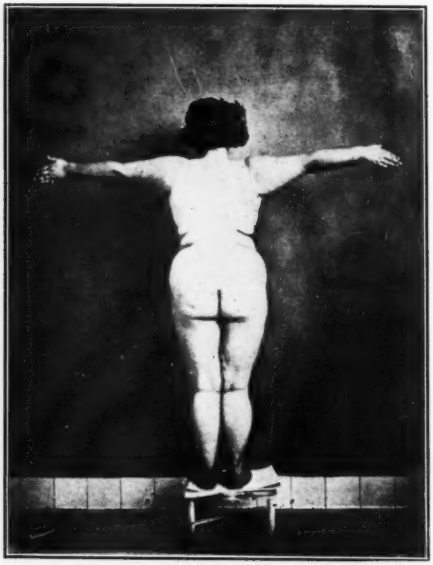


Fig. 12. Demonstrating the characteristic pituitary obesity.

SUMMARY OF CASES

The series studied consists of 1995 cases displaying endocrine abnormality, as manifest by their hormonic signs. Of this number 711 showed pituitary disturbance (285 purely pituitary, and 426 pluriglandular with pituitary involvement). The cases demonstrated and reported in detail above are representative types, showing more or less objective response to treatment, if we do not fall into "*post hoc ergo propter hoc*" error. There have been many failures, but there likewise have been very many apparent responses with careful clinical control. When, in a large series of cases, these responses in given types to given treatment occur often and with great regularity, we begin to get away from the coincidental and the *post hoc* idea, and approach conviction and a reasonable certainty that more than a casual relationship exists. Careful clinical observations are facts, as truly as biochemical, physiological, or pathological facts, though we admittedly often err in our interpretation. Inde-

pendent of the purely objective, there have been numerous subjective and apparently specific clinical responses to endocrine therapy that do not lend themselves to convincing visualization, especially for hypercritical minds. There have occurred relief of headaches, visual disturbances, psychic states, tachycardia, gastro-intestinal upset, constipation, dysmenorrhea, menstrual changes, decreased cerebration, incapacity, etc., that cannot be measured in millimeters or weighed in grams, but still they stand as clinical facts, so often recurring that they carry a modicum of conviction. Rest, change of climate, forced feeding, static sprays, hypnotism, Christian Science, blue lights, tamponades, I. Q. and S. or Elixir Taraxacum, and other forms of psychic treatment might accomplish the same results; but in most of the cases we speak of, several, and in some, all of these modes of treatment, had been tried without result.

We do not advocate endocrine therapy in so-called primary anemia, carcinoma, gastric ulcer, tonsillitis, aphthous stomatitis, or erysipelas, nor do we advise suprarenalectomy for epilepsy; but when, in a series of cases showing what we believe to be demonstrable hormonic evidence of endocrine disturbance, with subjective symptoms not due to other demonstrable causes, in which we repeatedly find response to indicated endocrine therapy, we feel that we must assume a casual relationship.

In the present state of our knowledge, it is no time for futile battle. Let us remember that vitriolic verbiage is no argument. Let us all, chemist, pathologist, physiologist, and clinician, realize that we are co-operative observers, all honestly and painstakingly marshalling facts that we may in harmony correlate, and thus further our knowledge in a perplexing, though interesting, field.

CONCLUSIONS

(1) There is remarkable discrepancy and lack of co-ordination in our available evidence concerning the function of the pituitary gland, considered either in its entirety or from the standpoint of its component lobes.

(2) There is little definite knowledge concerning the chemistry of the gland.

(3) The anterior lobe conforms to the requisites of a secretory gland, whereas the pars nervosa does not, being purely

nervous tissue; unless we take into consideration the pars intermedia as being the essentially secreting portion of the posterior lobe, realizing, too, that the pars intermedia is developmentally similar to the anterior lobe.

(4) We have no assurance that what we term posterior lobe extract, with apparently more demonstrable physiological effect, represents the true internal secretion of the gland, and can have no such assurance until the substance or active principle is demonstrated in the efferent blood or lymph of the gland, and no adequate available supply until this substance is synthesized and accurately standardized.

(5) Experimentation has taken insufficient account of the essential biological differences between the human being and experimental animals, a typical discrepancy being the consistent pressor effect as the result of pituitary extract in animals on first injection, and the frequent opposite effect in the human being, at least in our experience.

(6) Concerning the efficacy of the desiccated preparations of the gland, we have contradictory evidence. The value of pluriglandular therapy on the basis of a cell selectivity is being overpopularized; and, while one must realize the frequency of pluriglandular combinations and the almost absurd number of possible pathological combinations, sufficient attention must be paid to uniglandular therapy or the *rational* combination of glands based upon the presenting hormonic signs, and to the fact that pluriglandular imbalance may occur as the result of a lesion in one gland and may be restored by correcting the function of that particular gland.

(7) Therapy should be based upon the presenting hormonic signs, and, if these signs warrant, should be uniglandular, or even unilobar; and if other glands are apparently involved, an associated therapy should be instituted, but one based upon the presenting symptomatology.

(8) The literature has been flooded with reports concerning the response of isolated symptoms to pituitary therapy, without sufficient collateral detail concerning the type (osseous and genital makeup, obesity, dermal, chemical, or metabolic changes) or proper attempt at conformation to type.

(9) Upon what was deemed a judicious selection of evidence concerning the functions of the component lobes of the pituitary and their representative hormonic signs, a purely tentative classification was formulated, as it was felt that study along more specific lines would further our knowledge and enable us more quickly to negate or verify conflicting contentions concerning this gland.

(10) To secure the best results, therapy should be instituted early in the course of the disease, which implies early diagnosis. After pluriglandular involvement has occurred, a state usually resulting within a year, responses to therapy are less certain.

(11) The observation of a large number of cases to date, in which therapy was based upon the presenting symptomatology, has shown numerous responses, both subjective and objective—responses that have occurred so frequently that we have become convinced of more than a casual relationship and consider ourselves warranted in persisting in clinical studies along these lines.

BIBLIOGRAPHY

1. Cushing, H.: The pituitary body and its disorders, 1912.
   Concerning diabetes insipidus and the polyurias of hypophyseal origin. Bull Mass. Med. Soc., Medical Communications, 1913, xxiv, xxv, Part I; also, Boston M. & S. J., 1913, **163**, 901-910.
   Concerning the symptomatic differentiation between disorders of the two lobes of the pituitary body, with notes on a syndrome accredited to hyperplasia of the anterior and secretory stasis or insufficiency of the posterior lobe. Am. J. M. Sc. (Phila.), 1913, **145**, 313.
2. Bell, W. B.: The pituitary, 1919, p. 216.
3. Timme, W.: Clinical features accompanying changes in the sella turcica. J. Nerv. & Ment. Dis. (N. Y.), 1919, **50**, 460.
   Non-surgical treatment of pituitary disorders. Arch. Ophth. (N. Y.), 1920, **49**, 268-274.
   Endocrinologic aspects of some neurologic conditions. Arch. Neurol. & Psychiat., 1920, **3**, 601 (June 20).
4. Engelbach, W. & Tierney, J. L.: Pituitary polyuria (diabetes insipidus). Internat. Clin. (Phila.), 1920, **4**, S. 30, 123-180. (Tolerant dosage of pituitrin, p. 42.)
   Disorders of the pituitary gland (hypophysis cerebri). Tice's Practice of Medicine, 1922, viii. (Classifications pituitary disorders and hormonic signs, pp. 342, 354 & 413.)
   Ibid., Pituitary headache, p. 485.
   Ibid., Pituitary epilepsy, p. 553.
5. Engelbach, W.: Arterial hypertension associated with endocrine dyscrasia, J. Am. M. Ass. (Chicago), 1920, **74**, 1619-1624.
   Classification of disorders of the hypophysis. Endocrin. (Los Angeles), 1920, **4**, 347-365 (July-Sept.).
6. Schaefer, R.: Zur Rontgenbehandlung der Hypophysistumoren und der Akromegalie mit temporales Hemianopsie. Deutsche med. Wchnschr. (Berl.), 1919, **45**, 981; see also, Berl. klin. Wchnschr., 1919, **56**, 886.
7. Webster: Roentgen ray treatment of a case of early acromegaly. Arch. Radiol. & Electroth. (Lond.), 1920, **24**, 261.
8. Jaugeas: Contribution, nouvelle à la radiothérapie des tumeur hypophysaires. J. de radiol. et d'electrol. (Par.), 1919, **3**, 508.
9. Cavazzini-Bergamo: Due casi de tumore dell' ipofisi con sindrome acromegalica curati con e raggi X. Riforma med. (Napoli), 1920, **36**, 162.

10. Gramenga, A.: Un cas d'acromégali etraité par la radiothérapie. Rev. Neurol. (Par.), 1909, **17**, 15-17.
11. Béclère, A.: Radiotherapeutic treatment of tumors of the hypophysis, gigantism, and acromegaly. Arch. Roentg. Ray (Lond.), 1909-1910, **14**, 142.
12. Williams, T. A.: A case of subsidence through radiotherapy of neoplasm in the region of the hypophysis cerebri. J. Nerv. & Ment. Dis. (N. Y.), 1915, **42**, 159.
13. Terrien, F.: Le traitement par les rayons X destroubles visuels d'origine hypophysaire. Arch. d'opht. (Par.), 1916, **v**, 257-286.
14. Kupperle, V. S.: Ueber Strahlen-therapie bei Hypophysentumoren. Deutsche med. Wchnschr. (Berl.), 1915, **41**, 9-10.
15. Gunsett, A.: Ein mit Roentgenstrahlen behandelter Fall von Akromegalie. Strahalentherapie (Berl. u. Wien), 1913-15, **5**, 70.
16. Cauvin, C.: Acromegalie, tumeurs de l'hypophyse, troubles ventaires. Traitement organo- et radio-therapeutique guerison. Arch. d'opht. (Par.), 1912, **32**, 657.
17. Calamet, C. F.: Sur un cas de hemianopsie bi-temporale pas tumeur de l'hypophyse. Arch. d'opht. (Par.), 1916-17, **35**, 103.
18. de Lapersonne, F. & Cantonnet, A.: Troubles visuels produits par les tumeurs de l'hypophyse sans acromégalies. Arch. d'opht. (Par.), 1910, **30**, 65-91.
19. Quick, D.: Radium and x-ray in tumors of the hypophysis. Arch. Ophth. (N. Y.), 1920, **49**, 256.
20. Ranschburg, P.: Two cases of hypophyseal dystrophia adiposogenitalis treated by roentgen rays. Deutsche med. Wchnschr. (Berl.), 1921, **47**, 1291-1292 (Oct. 27); see also, Int. Med. & Surg. Survey, 1922. **3**, No. 1 (Jan.).
21. Ascoli, M. & Fagiuoli, A.: Effects of x-ray treatment of the hypophysis in bronchial asthma. Endocrin. (Los Angeles), 1920. **4**, 567-573 (Oct.-Dec.).
22. Fraenkel, M.: Reizdosenanwendung, ihre Bedeutung für die Röntgentherapie. München. med. Wchnschr., 1920, **67**, 528.
23. Kanavel, A. B.: Surgery of the hypophysis. Oxford Surg., 1919, **iii**, 438.
24. Hirsch: Traitement operatoire des tumeurs de l'hypophyse. Arch. Laryng. Otol. & Rhin., 1915, **37**, 20.
25. Moritz, M. A review of some of the more important factors involved in operation upon the hypophysis cerebri. Brit. J. Surg. (Bristol), 1913, **1**, 193.
26. Pardee, I. H.: Pituitary headaches and their cure. Arch. Int. Med. (Chicago), 1919, **23**, 174.
27. Blumgarten, A. S.: The endocrine factors in some common functional diseases. Med. Clin. N. Am. (Phila.), 1922. **5**, 1023 (Jan.); see also, Int. Med. & Surg. Survey, 1922, **3**, 809 (Apr.).
28. Glassburg, J. H.: Headache and dyspituitarism in the light of therapeusis. Med. Rec. (N. Y.), 1919, **96**, 461-463.
29. Beck, H. G.: Hypophyseal disorders with special reference to Froehlich's syndrome (dystrophia adiposogenitalis). Endocrin. (Los Angeles), 1920. **4**, 185-198.
30. von Dziembowski, S.: Dystrophia adiposogenitalis mit Myopathie. Deutsche med. Wchnschr. (Berl.), 1917, **43**, 654.
31. Lowenstein, P. S.: The relation of the pituitary gland to epilepsy. Am. J. M. Sc. (Phila.), 1922. **163**, 120 (Jan.).
32. Tucker, B. R.: The rôle of the pituitary gland in epilepsy. Arch. Neurol. & Psychiat. (Chicago), 1919, **2**, 192-200 (Aug.).
Pituitary disturbance in its relation to the psychoses of adolescence. J. Am. Ass. (Chicago), 1918, **71**, 330-332 (Aug. 3.).
33. Fliess, W.: Ein neuer Symptomencomplex der Hypophysis cerebri. Med. Klin. (Berl.), 1917, **13**, 966-970.
34. Weygandt, W.: Psychische störungen bei hypophysärer Fettsucht. München. med. Wchnschr., 1921, **68**, 1356-1357 (Oct. 21).
35. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie. Ztschr. f. klin. Med. (Berl.), 1908, **64**, 332-348.
36. Franchini, G.: Die Funktion der Hypophyse und die Wirkungen der Injektion ihres Extraktes bei Tieren. Berl. klin. Wchnschr., 1910, **47**, 613; 670; 719.
37. Falta: Drei Fälle von Diabetes insipidus, mit Pituitrin behandelt. Wien. med. Wchnschr., 1915, **45**, 1861-1863.
38. Schlesinger, W.: Ueber die Beziehung der Akromegalie zum Diabetes mellitus. Wien. klin. Rundschau, 1908, No. 15.

39. von Frankl-Hochwart, L. & Froehlich, A.: Zur Kenntnis der Wirkung des Hypophysins (Pituitrins, Parke, Davis & Co.) auf das sympathische und autonome Nervensystem. Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1910, **63**, 347-356.
40. Koopman, J.: Hypophyseal diabetes. Endocrin. (Los Angeles), 1919, **3**, 485 (Oct.-Dec.).
41. Steensma: Nederl. Tijdschr. v. Geneesk. (Amst.), 1914, **58**, (I), 2576.
42. Talqvist, T. W.: Untersuchungen über einen Fall von Diabetes insipidus. Ztschr. f. klin. Med. (Berl.), 1903, **49**, 181-192.
43. Meyer, E.: Deutsches Arch. f. klin. Med. (Leipz.), **83**, 1.
Ueber Diabetes insipidus. Deutsche Klinik (Berl. & Wien), 1910, **13**, Ergnzgabd., ii, 271-292.
Bemerkungen zu der Arbeit von Forschbach und Wever: Beogachtungen über die Harn- und Salz-Ausscheidung im Diabetes insipidus. Ztschr. f. klin. Med. (Berl.), 1912, **74**, 352-354.
44. Seiler, F.: Ueber des Wesen des Diabetes insipidus. Ztschr. f. klin. Med. (Berl.), 1907, **61**, 1.
45. Socin, C.: Ueber Diabetes insipidus. Ztschr. f. klin. Med. (Berl.), 1913, **78**, 294-308.
46. Finkelnburg: Ueber das Konzentrationsvermögen der Niere bei Diabetes insipidus nach organischen Hirnerkrankungen. Deutsches Arch. f. klin. Med. (Leipz.), 1910, **100**, 33-51.
47. Schwenkenbecher: Ein Beitrag zum ätiologischen Studium des Diabetes insipidus. München. med. Wchnschr., 1909, **54**, 2564-2568.
48. Forschbach & Weber: Beobachtungen über die Harn- und Salz-Ausscheidung im Diabetes insipidus. Ztschr. f. klin. Med. (Berl.), 1911, **73**, 221-239.
49. Spaether: Quoted from Moffett & Greenberger: Diabetes insipidus in children. Med. Rec. [etc.] (N. Y.), 1917, **92**, 487-495 (Sept.).
50. Ebstein: Beiträge zur Lehre vom Diabetes insipidus. Deutsches Arch. f. klin. Med. (Leipz.), 1909, **95**, 1.
51. Bernard, C.: Lèçons sur les propriétes physiologiques et les alterations pathologiques des liquides de l'organisme. (Paris), 1859, **1**, 397.
52. Eckhard: Beitr. z. Anat. u. Physiol., 1869, **iv**, 1, 153; 1870, **v**, 147; 1872, **vi**, 51.
53. Kahler: Ztschr. f. Heilk., 1886, **7**, 105.
54. Oliver & Schaefer: On the physiological action of extracts of the pituitary body and certain other glandular organs. J. Physiol. (Lond.), 1895, **18**, 277-279.
55. Magnus & Schafer: The action of pituitary extracts upon the kidney. J. Physiol. (Lond.), 1901-2, **27**, 9.
56. Schafer, E. A. & Herring, P. T.: The action of pituitary extracts upon the kidney. Phil. Tr. (Lond.), 1906, **cxcix**, 1-29; abst., Proc. Roy. Soc. Biol., 1906, **lxxvii**, S. B., 271.
57. Pentimalli & Quercia: Quoted from Barker & Mosenthal: On the control of the symptoms of diabetes insipidus by subcutaneous injections of extracts of the hypophysis cerebri (pars posterior and pars intermedia). J. Urol., 1917, **1**, 449 (Oct. 17).
58. van den Velden: Die Nierenwirkung von Hypophysenextrakten beim Menschen. Berl. klin. Wchnschr., 1913, **50**, 2083.
59. Motzfeldt: The pituitary gland and diuresis. Norsk. Mag. f. Lægevidensk. (Kristiania), 1915, 5.R., xiii, 1305-1376.
The pituitary body and renal function. Boston M. & S. J., 1916, **174**, 644-651.
Experimental studies on the relation of the pituitary body to renal function. J. Exper. M. (Balt.), 1917, **25**, 153-188.
60. Bab, H.: Die Hypophyse als Regulator der Diurese und des spezifischen Gewichts des Harnes. München. med. Wchnschr., 1916, **63**, 1685; 1721; 1758.
61. Biedl, A.: Innere Sekretion. 1913, 2 ed.
Quoted from Barker & Mosenthal: On the control of the symptoms of diabetes insipidus by subcutaneous injections of extracts of the hypophysis cerebri (pars posterior and pars intermedia). J. Urol., 1917, **1**, 449 (Oct. 17).
62. Fearnsides: Hypopituitarism, dystrophia adiposogenitalis, polyuria and polydipsia, etc. Proc. Roy. Med. (Lond.), 1916, Neur. Sec., **9**, 50.
63. Marañon & Pintos: Lesion traumatique pure de l'hypophyse. Syndrome adiposogenital et diabete insipide. Nouv. Icon. de la Salpêt. (Par.), 1916, **28**, 185.
64. Schuenemann: Ein Fall von traummatischen hypophysarer Fettsucht. München. med. Wchnschr., 1920 **67**, 198.

65. Houssay, B. A.: La Ciencia Med., Buenos Aires (Reprint. No date.) Los principas activos de los extractos hipopisiarios. (Estudio critico y experimental.) Prensa méd. argentina (Buenos Aires), 1915-16, **2**, 82; 91; 105.
Le principe actif des extraits hypophysaires. Rev. Soc. méd. argent. (Buenos Aires), 1911, 268.
The pituitary body and polyuria. Endocrin. (Los Angeles), 1918, **2**, 94-97.

66. Leschke: Beiträge zur klinischen Pathologie des Zwischenhirns. Ztschr. f. klin. Med. (Berl.), 1919, **87**, 201-279.

67. Claude & Lhermitte: Le syndrome infundibulaire dans un cas de tumeur du troisieme ventricule. Presse méd. (Par.), 1917, **25**, 417.

68. Olaechea: Sindrome hipofisiario de origen infundibular. An. Fac. de Med. (Lima), 1918, **2**, 103.

69. Rees, M. & Olmsted, W. H.: The use of pituitary extracts by mouth in the treatment of diabetes insipidus. Endocrin. (Los Angeles), 1922, **6**, 230-234 (March).

70. Mikhailoff, N. A.: Pituitary extract in enuresis. Russk. Vrach. (Petrograd), 1917, **16**, 417, abst., Endocrin. (Los Angeles), 1919, **3**, 89.

71. Bandler, S. W.: Some problems in obstetrics; caesarean section, high forceps, pituitary extract. Am. J. Surg. (N. Y.), 1916, **30**, 121-127.

72. Hofstätter, R.: Ueber die Verwendung von Hypophysensubstanzen bei der Behandlung der Amennorrhœ. Zentralbl. f. Gynæk. (Leipz.), 1920, **44**, 68.
Zur hypophysären Therapie des Morbus Basedowi. Ztschr. f. Geburtsch. u. Gynäk. (Stuttg.), 1918, **80**, 493.

73. Harvey, T. W.: Organotherapy. J. Med. Soc. N. Jersey (Newark), 1916, **13**, 452-461.

74. Pottenger, F. M.: Symptoms of visceral disease. 1919.

THE FUNCTION OF THE LOBES OF THE HYPOPHYSIS AS INDICATED BY REPLACEMENT THERAPY WITH DIFFERENT PORTIONS OF THE OX GLAND*

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The proper administration of an endocrine principle should correct an abnormality due to the deficiency of this principle.† In the tadpole four such rather sharply defined abnormalities result from early hypophysectomy,§ namely, (1) a slowed growth rate; (2) an underdevelopment of the interrenal bodies, parathyroids and thyroid with a consequent failure of the larva to metamorphose; (3) an abnormal condition of the pigment bearing cells resulting in albinism; and (4) a large and persistent fat organ which we are inclined to believe indicates a disturbance in metabolism. We should, by the proper administration of the hypophysis be able to correct these disturbances or, indeed, to go further and by the administration of the separate lobes determine which lobe when administered will remedy a particular abnormality and in this way analyze the functional nature of each of the lobes of this composite gland. The pituitary of the mammal (beef) lends itself readily to such an analysis.

Our experiments point to the conclusion that several principles, namely, that controlling (1) general body growth and the development of certain of the endocrine glands, (2) the behavior of the pigmentary system, and (3) the capacity of the fat organ to respond to nutritional conditions, are present in the hypophysis of the beef. Certain of these principles are found only in a single lobe; other principles are common to more than one lobe.

*Aided by a grant from the Elizabeth Thompson Science Fund. Read in modified form before the Association for the Study of Internal Secretions, June 25, 1923.

†We would hardly expect, however, to correct a condition of skeletal overgrowth; thus it would obviously be impossible to shorten the abnormally long bones of the extremities of the eunuch by the exhibition of testicular substance.

§By the term "pituitaryless" or "hypophysectomized" we refer to the loss of only the epithelial or buccal derivatives of this gland, not to the neural derivative, the posterior lobe. However, since in the specimens which have suffered the early loss of the buccal anlage of this gland the neural lobe is undersized, there is probably a deficiency in the secretion of this lobe also. Due to the metallic white appearance induced by hypophysectomy the animals are spoken of as "albinos."

In addition to determining the specific location of these principles in the bovine pituitary we have also inquired into their presence in the colloid found in the vestigial lumen of some of the glands. We also present some data on the stability or lability of these principles, obtained in our attempts to isolate the active principle or principles of the anterior hypophysis in somewhat purified form.

Preparation of Material. Fresh bovine glands secured not longer than six hours after the death of the animals were thoroughly washed and then sterilized in 50 per cent alcohol for five minutes. With sterile instruments and hands the *anterior lobe* of each pituitary was gently removed and the *pars intermedia* carefully separated from the posterior lobe. These lobes were rinsed in sterile salt solution to remove any contamination from each other. After slicing off and discarding a layer from the surface of the posterior lobe so as to make certain of its entire freedom from pars intermedia substance, the remaining (central) portion of the *pars nervosa* was used for the injection. It is possible to state that neither the anterior nor the posterior lobe was contaminated by the other lobes of the gland. It is not possible to state that a small amount of posterior lobe may not have been included with the pars intermedia, though, if any, such inclusion must have been very small. These lobes were ground up with sterile sand, diluted (3 pts. gland to 1 pt. saline), centrifuged, and the turbid supernatant fluid injected intraperitoneally. The colloid, after being carefully rinsed in sterile salt solution to remove any adherent juices, was treated in a similar manner and injected.

Mention will be made later of the treatment accorded the lobes to test the stability of the principles elaborated by them.

An abundance of tadpoles, *Rana boylei*, which we had hypophysectomized (some five hundred each season, this work having been carried on for two years) were available. These were supplied with a diet of muscle and lettuce and reared under conditions previously described (Smith, 1).

OBSERVATIONS

I. THE PARS ANTERIOR SUI GLANDULARIS

Injections of the anterior lobe substance correct all of the abnormalities above-mentioned as resulting from hypophysectomy, thus eliciting more responses, as will be seen, than does the injection of either of the other lobes of the pituitary.

It will be necessary here, in order to present our data, to describe the growth response separately from the endocrine response elicited by the injections of this lobe, a separation for which there appears to be justification, as will be pointed out at another time.

The Growth Response. It has been previously shown, Smith (2, 3), Allen (4, 5), that the hypophysectomized tadpole grows less rapidly than the normal controls. By injections of the an-

terior hypophysis a growth rate greatly in excess of the control is brought about (see table). The hypophysectomized tadpoles, after injections three times a week extending over a period of two to three months, exceed in volume their uninjected pituitaryless controls supplied with the same diet (muscle-lettuce) by approximately three times, and their uninjected, unoperated (normal) controls on the same diet by about two times. This effect transcends the limits of variability. The normal tadpole likewise gives an unmistakable response to anterior lobe injection, exceeding their controls in volume by about two times. An even greater response to these injections is given by thyroidectomized tadpoles which exceed in volume their thyroidless controls by approximately four times. The average volume of the injected thyroidless tadpoles at their maximum size exceeds the average volume of their uninjected unoperated (normal) controls at their maximum size (reached about a month earlier) by from five to seven times.

These growth results, although much more pronounced, are in accord with those obtained from transplantation experiments in amphibia as reported by Allen (6, 7) and Swingle (8), who found a growth acceleration to result from anterior lobe transplants in the tadpole. In the mammal (rat) an unquestioned growth acceleration results from the prolonged injection of fresh anterior lobe substance, "a mild degree of gigantism" being produced (Evans and Long, 9, 10).

It thus seems clear that the anterior lobe of the hypophysis carries a principle necessary for the maintenance of normal growth, an absence or profound reduction of which causes a slowing of the growth rate, and an excess of which accelerates growth, resulting in gigantism.

The Endocrine Response. The thyroid and interrenal bodies of the albino give a pronounced response to *injections* of anterior lobe substance. The atrophic thyroid of the hypophysectomized tadpole is repaired both functionally and structurally by these injections, the larvæ metamorphosing* (Smith and Smith, 11). The repair may pass the normal mark and

*During the final stages of metamorphosis these specimens frequently develop an edema. Specimens injected with anterior lobe substance which has been freed of a considerable amount of particulate matter and proteins usually do not develop an edema.

hyperplasia result. The scanty adrenal cortex of the albino becomes normal with injections of anterior lobe substance.

The *feeding* of anterior lobe does not elicit any response from the atypical glands of the albino (Smith, 1), actual injection of the substance being necessary in order to effect their repair. These effects on the thyroid from the injections of bovine anterior hypophyseal substance are in accord with transplantation experiments in amphibia [Allen (6), Swingle (8)].

The Pigmentary Response. Albinos injected with the anterior lobe darken perceptibly within a few hours after such injections; after several injections at intervals of two days each they become as dark as normal specimens.† In addition to this darkening in color tone, those injected with the anterior lobe exhibit a definite and unmistakable reddish tone which progressively becomes more pronounced during the metamorphic stages.

The miscroscopic examinations of the living specimens and of cutaneous whole mounts reveal the fact that both the melanophores and the xantholeucophores have lost the characteristics which they invariably display in the typical pituitary albino. The epidermal melanophores have increased in number to approximately that occurring in the normal specimen, have lost to a considerable degree their persistent contraction, and have become approximately normal in their melanin content. The free epidermal pigment (melanin) which is characteristically greatly reduced in the ablino is as abundant in these injected specimens as in the normal controls. It has been previously pointed out that in the typical pituitary albino the xantholeucophores, which form a double layer over most of the body, display a pronounced and persistent expansion and that to this expansion is referable the metallic white color so characteristic of the pituitary albino (Smith, 12). In the anterior lobe-injected pituitaryless tadpole these cells appear to be greatly contracted, a condition which apparently obtains in the normal, and are usually so described, a description with which we have heretofore agreed. Such a description, however, as a study of our injected albinos shows, has been based upon observations made upon the quanine content of these cells, the xanthine constituent being normally so slight in amount as to escape clear observation. In our hypophysectomized tadpole, injections of anterior lobe substance have caused a great increase in this latter constituent to which is due the above-mentioned reddish tone which these specimens display so that observations can now be made upon both the quanine and xanthine constituent of these cells with great reliability. Such observations show that while the refractile substance, quanine, is always centrally clumped, the lipochrome, xanthine, can be seen extending well out into the processes of spider-like cells, intermediate in shape, between

†This darkening in color from anterior lobe injections is not peculiar to the hypophysectomized tadpole. The depth of color is increased in the normal and thyroidless tadpole and a profound darkening results from the injection of this substance in the Colorado axolotl, these animals becoming jet black.

the corial and epidermal melanophores. With this definitely determined, the question immediately confronted us as to whether this condition is peculiar to the injected pituitaryless specimen or prevails also in the normal tadpole. We found this condition to obtain in the normal, where, however, the xanthine content is, of course, slighter in amount. The quanine thus may form an extensive sheet as in the typical albino or be clumped in a dotlike mass as in the injected pituitaryless or normal tadpole, without the xanthine undergoing the same changes. The different behavior on the part of these two pigments would appear to lend considerable support to the contentions of Schmidt (13, 14) that these two substances are borne by separate cells, paired and intimately associated, not by a common cell as Gaupp, Biedermann, Fuchs and others believe, and which caused them to use the term "xantholeucophore." For it seems improbable that two types of pigment within a cell would move independently of each other. The statement of Hooker (15) would appear to be as pertinent in this connection as in the discussion of cytoplasmic movement in the melanophore in which he pointed out that the assumption of an independent movement of two types of cytoplasm within a single cell is "unique in the animal kingdom" and states "the control by which such a process, alternately causing expansion and contraction of the one type of protoplasm within the other might go on indefinitely, is by no means clear."

The Behavior of the Fat Organ. The fat organ which attains an unusual size in the pituitaryless tadpole [see Fig. 60, Smith (1)], and persists even in starvation in contrast to the disappearance of this body in the normal tadpole under similar conditions is always reduced to normal dimensions in the hypophysectomized specimens which have been injected with anterior lobe substance. We have been inclined to believe that the enlarged condition of this "organ" is an indication of a disturbed metabolism and corresponds to the adiposity induced occasionally by operations on, or in the neighborhood of, the hypophysis of the mammal. If such a comparison be correct, then the injection of this lobe of the pituitary should reduce in the mammal the adiposity which may be instituted, experimentally, by operative procedures on the hypophysis.

II. THE PARS NERVOSA

Two of the abnormalties exhibited by the hypophysectomized tadpole, namely, the adiposity and albinism, are corrected by the injection of neural lobe substance, the latter being but imperfectly so, however. It must be emphasized here that we have injected pure pars nervosa substance uncontaminated by the intermediate lobe. The fat organ is reduced in size by the injection of pars nervosa in contrast to the large size normally obtaining in the pituitary albino.

What has been already described in regard to changes in

pigmentation with anterior lobe injection may be stated in regard to the responses of this system with posterior lobe injection, but with this modification, namely, that the return to a normal pigmentation does not develop so rapidly nor is it so complete as with anterior lobe injections. A greatly prolonged series of injections (3-4 months) may bring about a nearly normal coloration.

There is no effect upon growth, nor does the injection of posterior lobe cause any response in the thyroid or interrenal body of the albinos, the specimens remaining larval.

III. THE PARS INTERMEDIA

As with injections of the other two lobes of the pituitary the size of the fat organ is reduced by injections of the intermediate lobe. The immediate pigmentary response elicited by intermediate lobe injections is usually more pronounced than that given by either the neural or anterior lobe; the ultimate effect does not appear to transcend that given by the latter division of the gland. No unquestionable growth response is given, though the specimens usually become somewhat longer and relatively more slender than their untreated pituitaryless controls. This characteristic is distinctive for this treatment. No change is effected in the thyroid nor interrenal substance, legs do not develop and no other signs of metamorphosis are apparent.

IV. COLLOID

Injections of colloid substance produce a darkening of the albino, though a normal depth of pigmentation is not attained even when injections are carried out over a long period. No growth nor endocrine responses result and the specimens show no signs of metamorphosis. Our findings support the conclusion of Fenger (16) that the colloid of the vestigial lumen is a physiologically inert substance.

The stability of these principles as shown by various treatments. In our attempts to isolate the various principles of the anterior lobe of the beef we have found that the only principle which appears to retain its activity under all of the treatments, some of them most severe, to which we have subjected the anterior lobe substance is the principle evoking a reaction from the

pigmentary system.* A pronounced pigmentary effect was still secured after the anterior lobe had been boiled in distilled water, or in 0.3 per cent hydrochloric acid for several hours, a treatment which Hogben and Winton (17) found diminished the activity of the "melanophore stimulant" of the posterior lobe; the effectiveness persisted also after drying, taking no precaution to guard against oxidation. No endocrine nor growth responses were given by the anterior lobe after these treatments.

Treatment with alcohol, on the other hand, does not appear to destroy the endocrine principle. After extraction for 48 hours in absolute alcohol the supernatant fluid gave no effect upon the thyroid; however, a definite effect was given by injection of the precipitate. After extraction of the anterior lobe in 8 per cent alcohol for 24 hours the centrifuged supernatant fluid which had been freed from much of the proteins by this extraction gave a pronounced endocrine with a slight growth response, the specimens metamorphosing. The fate of the growth principal has not been ascertained in the alcohol residues, since the specimens absorbed with difficulty the particulate matter and the injections were terminated before the experiment had extended over a long enough period to determine definitely whether this principle were present or had been destroyed.

Both precipitate and supernatant fluid darkened the specimens. A pigmentary response has always been elicited by any hypophyseal substance which we have prepared from the anterior lobe and from both neural and intermediate lobes.

DISCUSSIONS AND CONCLUSIONS

The growth retardation which has been shown to result from hypophysectomy in the tadpole, appears to be definitely due to a deficiency of the glandular lobe of the pituitary. Grafts of the amphibian anterior lobe accelerate growth in the tadpole; injections of the bovine anterior hypophysis, as here shown, cause an overgrowth in either the hypophysectomized, normal or thyroidless tadpole. The specific growth stimulus which is thus given by this part of the hypophysis, the posterior lobe giving no acceleration and the intermediate lobe only a questionable one, would appear to demonstrate that the maldevelop-

*We have not tested the stability of this principle in either of the other lobes.

ments of the hypothalamus due to the early removal of the hypophysis (Smith, 1), plays no part in the growth retardation induced by these hypophysectomies and that they are due to a deficiency of anterior lobe secretion. This would appear to make it highly probable that the growth retardation induced by experimental hypophysectomies in the mammal [Crow, Cushing and Homans (18), Aschner (19)] is directly due to a quantitative reduction in the hormone of the anterior lobe and not, as suggested by Bailey (20), to any incidental injuries to the hypothalamus.* This conclusion is strongly supported by the fact that injections of anterior lobe substance induce a "mild degree of gigantism" in the rat (Evans and Long, 9, 10).

Anterior lobe substance exercises a definite control over at least the thyroid and interrenal glands. Extirpation experiments, obviously, in the tadpole would not make it certain which division of the pituitary exerts this influence, since the anlage ablated is destined to form both intermediate and anterior lobes, and prevents the normal development of the neural lobe. Since injections of the bovine anterior lobe repair the underdeveloped glands, the tadpole then metamorphosing (Smith and Smith, 11), while injections of neither of the other two divisions effects such a repair, it is clear that the anterior lobe alone exerts this reparative or constructive influence on these glands.

It would appear to us that this response of the thyroid to anterior lobe injections is an expression of a constructive influence which the glandular lobe of the hypophysis exercises. A lack of this influence (or stimulation) is apparently seen in the failure of the pituitaryless tadpole to grow at a normal rate and to develop a normal endocrine system. This can be corrected or "over-corrected" with a consequent gigantism and thyroid hyperplasia by anterior lobe injections. It appears that the stimulus to lutein cell formation in the rat which Evans and Long (10) have shown is effected by anterior lobe injections, thus indirectly inhibiting oestrus, may be an expression by this gland of a general constructive or stimulative influence upon the glands of internal secretion.

We have seen that the ablation of the buccal hypophysis brings about a profound derangement in the pigmentary system of the tadpole, the specimens becoming albinous. Skin trans-

*Any direct operative injury to the hypothalamus is absolutely precluded by the nature of our hypophysectomies.

plants have shown that this albinism is due to an alteration in the body fluids, probably of an endocrine origin and not to an altered nervous connection (Smith, 21; 1).

Investigators have referred any pigmentary influence which may be exerted by the hypophysis to the pars intermedia [Atwell (22, 23), Smith (1), Allen (6, 7), Swingle (8), Hogben and Winton (17)]. In this paper we have shown that the injection of each of the three lobes of the bovine pituitary and of the colloid alters the state of contraction of these cells and increases the pigment content of some of them.

The profound effect which this principle has on pigment metabolism, and the broad distribution which it enjoys in the bovine pituitary would make it seem highly probable that it must play some significant rôle in the body of the mammal.* It is surprising that pigmentary disturbances in pituitary dystrophies are not more frequently described.

The enlarged fat body of the albino, we have found, is reduced to normal dimensions by the administration of any one of the three lobes of the pituitary, a reduction which we have not been able to effect by inanition or thyroid administration. This specific response of the fat body appears to demonstrate that its enlarged condition in the hypophysectomized tadpole is due to a pituitary deficiency and not to any abnormalities of the hypothalamus, which develop secondarily. It is pertinent here again to mention that any direct operative injury to the infundibular region is absolutely precluded by the nature of our hypophysectomies.

We realize that these findings in regard to the response of the fat body of the pituitaryless tadpole do not justify us in stating that the adiposity induced occasionally from operations on the pituitary region of the mammal is due to a pituitary deficiency. The gap between the two forms is wide and the "adiposity" of the hypophysectomized tadpole may not be analogous

*The fact that this principle alters the state of *contraction* of the pigment cells would not indicate that it has specifically to do with pigment changes in the mammal. Thus adrenin, which contracts the corial melanophores (Lieben, 24), alters the state of contraction of smooth muscle also, a fact which has led Spaeth (25) to believe that the melanophore is a disguised type of smooth muscle. Hogben and Winton (17) have shown that there are certain similarities in the behavior of the "melanophore stimulant" and of the uterine stimulant of the posterior lobe when treated with HCl, their action differing from the pressor substance of this lobe. The fact, however, that this principle influences the *metabolism* of epidermal pigments would appear to make it of importance in the mammal.

D

TABLE SHOWING THE MAXIMUM, MINIMUM AND AVERAGE VOLUMES AND LENGTHS (BOTH TOTAL AND OF LEGS) OF NORMAL, HYPOPHYSECTOMIZE AND THYROIDLESS FROG LARVAE WITH VARIOUS TREATMENTS

Type.....	Hypophysectomized				Hypophysectomized				Normal				Normal				Thyroidless				Thyroidless			
Injection.....	Pars anterior				None				Pars anterior				None				Pars anterior				None			
	Length in mm.		Vol. in cc.	No. of Specs	Length in mm.		Vol. in cc	No. of Specs	Length in mm.		Vol. in cc.	No. of Specs	Length in mm.		Vol. in cc.	No. of Specs	Length in mm.		Vol. in cc.	No. of Specs	Length in mm.		Vol. in cc.	No. of Specs
	Total	Leg			Total	Leg			Total	Leg			Total	Leg			Total	Leg			Total	Leg		
July 2.....	33-34	None	.....	..	29-31	None	.....	..	28-30	.....	.....	..	29-30	.....	.....	..	30-35	.....	.....	..	32-34	None	.....	..
	33	.....	.....	11	30	.....	.....	10	30	2	.....	11	30	2	.....	10	34	1.5	.....	12	33	.....	.....	10
July 20.....	34-40	.....	.....	..	30-35	None	.....	..	36-39	.....	.....	..	33-39	.....	.....	..	38-45	None	.....	..	37-41	None	.....	..
	39	1	.....	11	33	.....	.....	9	37	4	.....	7	36	4	.....	10	40	*5	.....	7	39	.....	.....	10
Aug. 6.....	34-45	1.5-3	.....	..	30-36	None	.....	..	41-44	7-10	.....	..	34-43	3-7	.....	..	43-52	None	.....	..	39-42	None	.....	..
	43	2	.....	11	33	.....	.....	9	42	8	.....	6	38	4.5	.....	10	47	.....	.....	2	40	.....	.....	10
Sept. 2.....	47-59	8-17	0.9-1.6	..	31-41	None	.3-.5	..	44-53	17-22	1-1.5	..	38-45	6-18	.4-.85	..	53-59	None	1.3-1.9	..	45-52	None	.....	..
	52	13	1.3	9	36	.....	.45	6	49	20	1.2	6	43	11	0.66	9	56	.....	1.6	2	48	.....	.....	10
Sept. 23.....	52-64	17-23	1.2-2	..	.....	.....	.....	..	.....	.....	.....	..	40-46	7-25	.....	..	65-67	.....	1.9-2.3	..	52-59	None	0.7-1.1	..
	59	20	1.6	5	.....	.....	.....	..	.....	.....	.....	..	43	17	.....	8	66	2.5	2.1	2	57	.....	0.9	10
	Metamorphosing				Series discontinued				All specimens metamorphosed				One specimen metamorphosed											
Oct. 20.....	.....	.....	.....	..	.....	.....	.....	..	.....	.....	.....	..	.....	.....	.....	..	77-79	.....	4	..	55-67	None	0.8-1.2	..
	.....	.....	.....	..	.....	.....	.....	..	.....	.....	.....	..	.....	.....	.....	..	78.2	2.5	4	2	59	.....	1.1	10

Type	Hypophysectomized	Hypophysectomized	Hypophysectomized	Hypophysectomized	Hypophysectomized
Injection	None	Pars intermedia	Pars neuralis	Pars anterior	Colloid
	Length in mm. / Vol. in cc. / No. of Specs	Length in mm. / Vol. in cc. / No. of Specs	Length in mm. / Vol. in cc. / No. of Specs	Length in mm. / Vol. in cc. / No. of Specs	Length in mm. / Vol. in cc. / No. of Specs
Aug. 30	Total 37–40 / Leg 39 / None / ..... / ..... / 8	Total 37–38 / Leg 37 / None / ..... / ..... / 8	Total 36–38 / Leg 37 / None / ..... / ..... / 8	Total 35–41 / Leg 38 / None / ..... / ..... / 8	Total 35–37 / Leg 36 / None / ..... / ..... / 10
Sept. 23	36–45 / 39 / None / ..... / 0.5–0.6 / 0.55 / 7	41–44 / 43 / None / ..... / 0.5–0.8 / 0.66 / 8	35–46 / 39 / None / ..... / 0.3–0.8 / 0.5 / 8	41–47 / 44 / ..... / 1.5 / 0.7–0.8 / 0.7+ / 8	33–38 / 36 / None / ..... / .4–.56 / 0.46 / 9
Oct. 20	39–49 / 43 / None / ..... / 0.4–0.8 / 0.62 / 5	48–52 / 50 / None / ..... / 0.8–1.1 / 0.85 / 8	42–52 / 46 / None / ..... / 0.5–0.95 / 0.65 / 6	52–60 / 58 / 1.5–5 / 3+ / 1–1.8 / 1.5 / 8	36–41 / 39 / None / ..... / 0.45–0.7 / 0.52 / 4
Nov. 3	43–45 / 42 / None / ..... / 0.65–0.85 / 0.73 / 3	50–53 / 51 / None / ..... / 0.75–1 / 0.9 / 5	44–47 / 46 / None / ..... / 0.55–0.6 / 0.58 / 3	60–66 / 63 / 3–12 / 7 / 1.9–2.05 / 2 / 7	39–41 / 40 / None / ..... / 0.5–0.55 / .52 / 2
Nov. 17	.... / .... / ..... / ..... / ..... / Discontinued	48–59 / 49 / None / ..... / 0.7–1 / 0.9 / 4 Discontinued	.... / .... / ..... / ..... / ..... / Discontinued	58–67 / 63 / 9–18 / 13 / 1.5–2.2 / 1.9+ / 7 Metamorphosing	.... / .... / ..... / ..... / ..... / Died

*The specimens which developed legs over 3 mm. in length showed, when sectioned later, small thyroid remnants. These specimens are not included in the remainder of the column.

to the adiposity in the adiposo-genital syndrome of the mammal. Yet the probability of an identical causative factor in the two animal forms should prevent us from too hastily casting aside the earlier concept that the adiposity in this syndrome was due to a pituitary deficiency and substituting in its place the idea that all responsibility for this condition can be laid at the door of the hypothalamus, as some investigators have been inclined to do. Since the principle which will diminish the size of the fat body of the pituitaryless tadpole is present in each of the three lobes of the hypophysis, it is not surprising that adiposity does not usually develop in the mammal in partial anterior lobe removals or in posterior lobe ablations.

SUMMARY

The intraperitoneal injection of different portions of the bovine hypophysis in the hypophysectomized tadpole gives the following results:

1. Pars anterior brings to normality the four deficiencies resulting from hypophysectomy in that it accelerates the growth rate; induces a normal depth of pigmentation; repairs the atrophic thyroid and interrenal bodies, the specimens metamorphosing; and reduces to normal dimensions the fat organ. The normal and thyroidless tadpoles when injected with anterior hypophysis show an acceleration in their growth rate, attaining an unusually large size, and display an increased depth of pigmentation.

2. Pars intermedia corrects the pigment upset and reduces the size of the fat organ.

3. Pars neuralis elicits a moderate pigmentary response and reduces the size of the fat organ.

4. Colloid induces a slight response in the pigmentary system.

Of the various principles in the bovine anterior hypophysis that evoking a response in the pigmentary system appears to be stable, withstanding drying, severe heat, and certain chemical treatments; while those principles accelerating growth and reaction with the endocrine system are more labile, remaining active, however, after treatment with alcohol.

BIBLIOGRAPHY

1. Smith, P. E.: The pigmentary, growth and endocrine disturbances induced in the anuran tadpole by the early ablation of the pars buccalis of the hypophysis. Am. Anat. Mem. (Phila.), 1920, No. 11.
2. ——: Experimental ablation of the hypophysis in the frog embryo. Science (Utica), 1916, n.s. **44,** 280-282.
3. ——: The effect of hypophysectomy in the early embryo upon the growth and development of the frog. Anat. Record (Phila.), 1916, **11,** 57-64.
4. Allen, B. M.: Extirpation experiments in Rana pipiens larvae. Science (Utica), 1916, n.s. **44,** 755-757.
5. ——: Effects of the extirpation of the anterior lobe of the hypophysis of Rana pipiens. Biol. Bull. (Woods Hole), 1917, **32,** 117-130.
6. ——: The effects of transplantation of the several parts of the adult hypophysis into tadpoles of Rana pipiens. Anat. Record (Phila.), 1921, **20,** 192-193.
7. ——: Experiments on the transplantation of the hypophysis of adult Rana pipiens to tadpoles. Science (Utica), 1920, n.s. **52,** 274-276.
8. Swingle, W. W.: The relation of the pars intermedia of the hypophysis to pigmentation changes in anuran larvae. J. Exper. Zoöl. (Phila.), 1921, **34,** 119-141.
9. Evans, H. M. & Long, J. A.: Characteristic effects upon growth, oestrus and ovulation induced by the intraperitoneal administration of fresh anterior hypophyseal substance. Anat. Record (Phila.), 1922, **23,** 19.
10. ——: Ibid. Proc. Nat. Acad. Sc. (Balt.), 1922, **8,** 38-39.
11. Smith, P. E. & Smith, I. P.: The repair and activation of the thyroid in the hypophysectomized tadpole by the parenteral administration of fresh anterior lobe of the bovine hypophysis. J. Med. Research (Boston), 1922, **43,** 267-283.
12. Smith, P. E.: The pigment changes in frog larvae deprived of the epithelial hypophysis. Proc. Soc. Exper. Biol. & Med. (N. Y.), 1919, **16,** 74-78.
13. Schmidt, W. J.: Ueber die sog. Xantholeucophoren beim Laubfrosch. Arch. f. mikr. Anat. (Bonn), 1919, **93,** 93-117.
14. ——: Ueber das Verhalten der verscheidenartigen Chromatophoren beim Farbenwechsel des Laubfrosches. Ibid, 1920, **93,** 414-455.
15. Hooker, D.: Amoeboid movement in the corial melanophores of Rana. Am. J. Anat. (Phila.), 1914, **16,** 237-250.
16. Fenger, F.: The composition and physiological activity of the pituitary body. J. Biol. Chem. (Balt.), 1916, **25,** 417-422.
17. Hogben, L. T. & Winton, F. R.: Studies on the pituitary. I. Biocem. J. (Cambridge), 1922, **16,** 619-630.
18. Crow, Cushing & Homans: Experimental hypophysectomy. Johns Hopkins Hosp. Bull. (Balt.), 1910, **21,** 126-169.
19. Aschner, B.: Uber die Beziehungen zwischen Hypophysis and Genitale. Arch. f. Gynæk. (Berl.), 1912, **97,** 200-228.
20. Bailey, P.: Die funktion der Hypophysis cerebri. Ergebn. d. Physiol. (München), 1922, **20,** 162-206.
21. Smith, P. E.: Upon the experimental exchange of skin transplants between normal and albinous larvae. Proc. Soc. Exper. Biol. & Med. (N. Y.), 1919, **16,** 81-82.
22. Atwell, W. J.: On the nature of the pigmentation changes following hypophysectomy in the frog larvae. Science (Utica), 1919, n.s. **49,** 48-50.
23. ——: Further observations on the pigment changes following removal of the epithelial hypophysis and the pineal gland in the frog tadpole. Endocrin. (Los Angeles), 1921, **5,** 221-232.
24. Lieben, S.: Uber die Wirkung von Extrakten chromaffinen Gewebes (Adrenalin) auf die Pigmentzellen. Centralbl. f. Physiol. (Leipzig & Wien), 1906, **20,** 108-117.
25. Spaeth, R. A. Evidence proving the melanophore to be a disguised type of smooth muscle cell. J. Exper. Zoöl. (Phila.), 1913, **20,** 193-215.
26. Bailey, P. & Bremer, F.: Experimental diabetes insipidus. Arch. Int. Med. (Chicago), 1921, **28,** 773-803.

Book Reviews

EIN EXPERIMENTEEL KRITISCH ONDERZOEK OVER DE OEDEEMTHEORIE VAN EPPINGER. S. van Creveld, Amsterdam, 1922. 128 p.

In 1917 Eppinger published his book, "Zur Pathologie und Therapie des menschlichen Oedems." In it he states, among many other things, his theory that diuresis does not depend upon the kidney alone. In the regulation of water and salt metabolism the complex of the intercellular spaces in the tissues has a function just as important or even more important than the kidney. The most effective drugs that act, not on the kidneys, are the thyroid preparations; these are often very effective in seemingly incurable cases of edema. Thyroid medication, Eppinger believed, acts by breaking down the proteins of the edema fluid. Eppinger's statements have been generally accepted. Van Creveld, however, does not agree with him. On the basis of numerous experiments he concludes that the hormone of the thyroid acts directly upon the kidney. It also increases protein metabolism and the resulting metabolites cause an increase of diuresis. Those who have read Eppinger's book should read this critique by van Creveld. Unfortunately it is written in Dutch, thus preventing most investigators from reading it.—J. K.

IL MORBO DI RECKLINGHAUSEN. N. Samaja, Milano, 1919. Società editrice libraria. 85 p.

Recklinghausen's disease is believed by some to be due to endocrine disorders. The adrenals, especially, are often reported to be involved. Various cases have been described which have been markedly improved by organotherapy, although each investigator seems to have used a different preparation. Samaja's book gives an excellent review of the known data on this subject. Some splendid illustrations and an excellent bibliography increase the value of the book.—J. K.

CONTRIBUCION AL ESTUDIO DE LOS TUMORES DE LA HIPOFISIS. Wehrhahn R. Alejandro. Santiago de Chile. Imp., Lit. y Enc. "La Illustracion," Calle Moneda, 873. 1922. 175 p. with illustrations.

Reviewed in Am. J. Roentgenol., **9**, 834, by James T. Case, who pronounces it a splendid work on the clinical diagnosis and treatment of tumors of the hypophysis.—R. G. H.

THE THYROID GLAND. George W. Crile, M.D., and Associates at the Cleveland Clinic, Ohio. Philadelphia, 1922. W. B. Saunders Company. 228 p.; 106 illustrations.

Reviewed in Am. J. M. Sc. (Phila.), 1922, **164**, 750.

DIE OEDEMKRANKHEIT. Prof. Dr. A. Schittenhelm & Prof. Dr. H. Slecht. Berlin, 1919. Julius Springer. 103 p.

The studies reported in this book were completed but publication was forbidden by the military censor.

The edema problem has been of special endocrine interest since Eppinger's investigations concerning the rôle of the thyroid in the pathogenesis of that disorder. Schittenhelm and Slecht have carefully studied the metabolism and the influence of *thyroidin, adrenalin* and *hypophysis* on water and salt metabolism in cases of edema. Excretion of water and salt, when not given in large quantities, seems normal. However, thyroidin markedly hastens the excretion of NaCl and water, although in health it has practically no influence. The influence of other drugs, such as adrenalin and hypophysis, is shown in many tables and curves. The book is easy and pleasant to read, but nearly impossible to abstract. The reviewer recommends it very highly to all who are interested in edema. It is greatly superior to much of the endocrine literature.—J. K.

INTERNAL SECRETIONS AND THE DUCTLESS GLANDS. Swale Vincent. Second Edition. London, 1922, E. Arnold & Co., N. Y., Longmans, Green & Co. 422 p. 8°.

Many endocrinologists are already familiar with Professor Vincent's book through the widespread use of the first edition of it.

The monograph is written from a standpoint indicated in the introductory chapter: "It must be confessed," the author says, "that we do not know the functions of any one of the ductless glands in the same definite way in which we know the functions of, for example, the lungs or the pancreas. Owing to the lack of boundaries and the absence of precise exploration in many regions, the territory of internal secretion has been invaded by some irresponsible exploiters. The time has arrived for us to take our bearings and ascertain our precise position with regard to the subject. In doing this, every effort will be made to avoid dogmatism, even at the risk of losing, or hesitating

to accept, some tempting and plausible theories." The chapter on methods concludes: "It seems to the present writer that one of the methods which will yield the most valuable results in the near future is the oldest of all—namely, careful study of clinical conditions and a patient investigation of pathological anatomical findings. Now that the microscopical structure and the comparative anatomy has been worked out with some completeness, and the results of extirpation experiments and the action of organ extracts fairly well known, pathologists may return to the problems with a better foundation of knowledge and fresh hopes for future discovery."

While many worth-while contributions in the enormous mass of the endocrine literature have necessarily been omitted, the author has on the whole chosen his material judiciously. In the opinion of the reviewer, the book is the best of its scope in the English language for the student wanting a good general command of the subject of endocrinology.—R. G. H.

Die Konstitutionelle Disposition zu Inneren Krankheiten. Dr. J. Bauer. Second Edition. Berlin, 1921, J. Springer. 650 p.

Much space is devoted to endocrine factors and their importance in determining constitutional make-up. There is much to be learned from every page, and no one who reads this splendid book will regret the time devoted to it.—J. K.

Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes. Hugh Maclean, M.D., D. Sc., M.R.C.P. Constable & Co. 159 p., 13 charts, 9 figures. Price, 12s.

Reviewed in Irish J. M. Sc. (Dublin), 1922, 5s., 484.

Handbuch der Biologischen Arbeitsmethoden. Hrsg. v. Emil Abderhalden. Abt. V., Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus, Tl. 3 A, H. 3, Lief. 69. Curt Herbst, Günther Hertwig, Benno Romeis & Hermann Braus. Urban u. Schwarzenberg, 1922, Berl. u. Wien. pp. 441-538.

Reviewed in Ber. ü. d. ges. Physiol., **15**, 357.

Abstract Department

Sensitization of the Trendelenburg frog preparation for the determination of ADRENALIN (Sensibilisierung des Trendelenburgschen Frosch-präparates zur Adrenalinmessung). Alday-Redonnet (T.), Biochem. Ztschr. (Berl.), 1920, **110**, 306-318.

The addition of 0.1% more KC1 to the perfusing Ringer's solution markedly sensitizes the Trendelenburg preparation. An alkaline reaction of the perfusion fluid has the same effect. The optimum lies around $cH=10^{-8.5}$ in phosphate buffer solution. The spontaneous sensitization which occurs in the usual preparation is due to a diminished acidity.—F. S. H.

ADRENAL insufficiency (Breves consideraciones sobre insuficiencia surrenal). Alvarez (W.), Semana méd. (Buenos Aires), 1922, **29**, 869-872 (October 26).

The author diagnosed adrenal insufficiency in a case of acute peritonitis, one of "typomalaria" and one of chronic malaria. In the first two cases adrenalin ameliorated the symptoms.—B. A. H.

Intracardial ADRENIN injection for acute heart failure (Intrakardiale Adrenalininjektion bei akuter Herzlähmung). Baumann (E.), Schweiz. med. Wchschr. (Basel), 1923, **53**, 198-200 (February 22).

Report of 2 cases of heart failure of young children successfully treated. The recommended dosage is 0.5 cc. "adrenalin" for children under six months of age and proportionately larger doses up to 1.25 cc. for adults.—R. G. H.

The cholesterol and lipoid phosphorus contents of the blood of rabbits before and after SUPRARENALECTOMY. Baumann (E. J.) & Holly (O. M.), J. Biol. Chem. (Baltimore), 1923, **55**, 457-475.

Rabbits were suprarenalectomized, usually in two stages, and the basal metabolism, blood lipoids and other determinations made frequently. The results show that there is no evidence for the hypothesis that the adrenals are the seat of cholesterol formation. Nor is there any reason to suppose that the glands act as a storehouse for cholesterol.—F. S. H.

Sudden death in a soldier presenting marked fibrosis of the ADRENALS (Morte subite chez un militaire presentant des lesions de surrenalite sclereuse). Bazin, J. de méd. et de chir. prat. (Paris), 1918, **89**, 735-738.

This is a report of the case of a soldier aged 35 years, who after an attack of "grippe" complained of fatigue, followed by nausea and vomiting. There was no pigmentation of the skin. "Ligne blanche" was absent. Death occurred suddenly, after a short period of dyspnoea and cyanosis. At postmortem examination marked fibrosis of both adrenals was found. Bazin thinks that adrenals which are the site of such a chronic inflammatory process may be a factor in sudden deaths after acute infections like "grippe."—J. P. S.

A case of intoxication by ADRENALIN (Ein Fall von Adrenalinvergiftung). Bornstein, Klin. Wchnschr. (Berl.), 1922, **1**, 1484; see also Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1400.

Ten years ago a doctor intravenously injected into himself 1 mg. of adrenalin. After severe collapse, Bright's disease developed; orthostatic albuminaria remained for some time, but at the time of the report the only symptom was renal glycosuria.—J. K.

Treatment of epileptic spasms by ablation of an ADRENAL (Zur Behandlung der epileptischen Krämpfen mit Exstirpation einer Nebenniere nach Brüning). Borszéky (K.), Zentralbl. f. Chir. (Leipz.), 1922, **49**, 1053-1057.

The author removed an adrenal in each of 9 cases of epilepsy. The operation seems to have no evil consequences. Although not one case was cured after operation, there was usually temporary improvement. The author recommends the ablation of the right adrenal, since it is often heavier than the left.—J. K.

Incoercible vomiting of pregnancy with acidosis. ADRENALIN carbohydrate treatment. Therapeutic abortion. Psychic troubles. Cure (Vomissements incoercibles de la grossesse avec acidose. Echec du traitement hydrocarboné-adrénaline. Avortement thérapeutique. Troubles psychiques. Guérison). Cathala & Biancani, Gynéc. (Par.), 1922, **24**, 615-616.

Syphilis of the ADRENALS. Deaderick (W. H.), Am. J. Syph. (St. Louis), 1923, **7**, 72-82.

An excellent review of the literature and report of a case. A woman of 40 with positive Wassermann reaction developed, among other changes, weakness, slight hypotension, anemia and very marked pigmentation. A diagnosis of probable Addison's disease was made. After 3 weeks' treatment with mercury and adrenal gland substance the systemic symptoms, but not the pigmentary condition, were improved. A month after discharge the patient reported that the discoloration was fading.—R. G. H.

Effect of muscular activity on perfused ADRENIN. Hoskins (R. G.) & Durrant (E. P.), Am. J. Physiol. (Balt.), 1923, **63**, 404-405 (Proc.).

The systemic reactions to adrenin perfused through the limb of a dog or cat are not decreased after severely fatiguing the limb. It is suggested that adrenin is probably a respiratory catalyst. —T. C. B.

ADRENAL syphilis (Syphilis das glandulas suprarrenaes). Figueredo (C. B. de), Comunic. 3a Conferencia de Higiene Microbiologia e Patologia, Montevideo, 1923.

Description of 90 cases of syphilis, with histologic study of the different organs and especially of the adrenals, the latter showing lesions in 75 cases. The following disorders were seen: lymphatic and plasmatic infiltrations, para- or sub-capsular, rarely in the cortex (63%); thickening of the gland with perivascular infiltration (31%); and circumscribed fibrosis (3.3%). The spirochetes were found in the zones of leucocyte infiltration. The frequent appearance of adrenal lesions in syphilitic subjects (83%) should render this gland of valuable diagnostic assistance at autopsy.—B. A. H.

Colorimetric and pharmacologic evaluation of the ADRENALIN content of the ADRENALS (Die Kolorimetrische und pharmakologische Auswertung des Adrenalingehalts der Nebennieren). Frowein (B.), Biochem. Ztschr. (Berl.), 1923, **134**, 559-666.

The colorimetric method gives too high results and should be replaced by the blood-pressure method.—F. S. H.

Urine acidity after the injection of ADRENALIN chloride. Hubbard (R. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 187-189.

The tests were made on the author. Two tablets were given showing the effects on the blood, breath, and urine after 1 cc. of a 1-1000 solution was injected subcutaneously. There was only a slight change in the acidity of the urine.—J. C. D.

The influence of the injection of ADRENALIN into the subarachnoid cavity on body temperature. Ikeda (S.), Chugwai Iji-Shimpo, 1922, No. 1013.

The subarachnoid injection of adrenalin results in a slow and gradual rise of the body temperature.—Jap. Med. World, **2**, 325.

Calcium content of the serum after ADRENALIN injection. Inouye (T.), Tokyo Igakkai Zasshi, 1922, **36**, No. 6 (June); abst., Jap. Med. World (Tokyo), 1922, **2**, 331.

Although there occur quantitative changes in the calcium contents of the urine after adrenalin injections, there develop no changes in the calcium contents of the blood as they have been estimated at 10, 15 and 30 minutes after the injection.—R. G. H.

The musculature of the venous walls in the human suprarenal and its relation to the action of ADRENALIN. Kashiwagi (M.),

Nisshin Igaku, 1922, **11**, No. 10 (June); abst., Jap. Med. World (Tokyo), 1922, **2**, 327.

The author points out in the parenchyma of the suprarenal capsules the presence of groups of longitudinal smooth muscle fibers in the venous walls which are connected directly with the perivascular membrane. These are the results of the continuous stimulation by adrenalin and they become more and more prominent as the age advances.—R. G. H.

Anencephalia and the ADRENALS (Anenzephalie und Nebenniere). Kohn (A.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1666.

Anencephalia and hypoplasia of the adrenals are sometimes found together. The author believes that primary to hypoadrenalism a change is always found in the hypophysis of anencephalic monsters (no infundibulum and no pars nervosa); in the pars anterior the oxyphil cells are rare, and many peculiar large basophil cells are found. The adiposity of anencephalic subjects may be explained also by hypophyseal changes.—J. K.

Blood features after the injection of ADRENALIN, especially on the numerical changes of the blood plateletts. Kubo (K.), Nippon-No-Ikai, 1922, **12**, No. 21, No. 22; cit. Jap. Med. World (Tokyo), 1922, **2**, 328.

Diagnostic importance of glycosuria after injection of ADRENIN in pregnancy (Der diagnostische Wert der Adrenalinglykosurie für die Schwangerschaft). Küstner (H.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1340-1341.

During the first seven months of pregnancy 91% of all women have renal diabetes. To prove its existence the author recommends the so-called Brinnitzer-Roubitschek test. The patient takes on the empty stomach 10 gm. of glucose, dissolved in 150 to 200 cc. of water; twenty minutes later 0.5 mg. of adrenalin is injected subcutaneously. Blood sugar estimations are made before the test is begun and ½, 1 and 1½ hours after the injection. If after 1½ hours no glucose is found in the urine, examination is made 2 and even 3 hours after the injection. Usually in ¾ to 1½ hours sugar is found in the urine. The average maximum blood sugar is 0.140%.—J. K.

The ADRENALS in morphin intoxication (Suprarrenales e intoxicacion morfinica). Lewis (J. T.), Semana méd. (Buenos Aires), 1922, **29**, 309-311 (August 10); cit., J. Am. M. Ass. (Chicago), 1922, **79**, 2042.

(ADRENIN) Pharmacodynamic reactions of erectile tissue and the dorsalis penis artery. Macht (D. I.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 90-91.

Material from the dog was studied by methods devised by the author. The tissues studied responded to **adrenin** and ergotoxin but not to "parasympathetic" poisons. The author concludes that these tissues are innervated by the thoracico-lumbar sympathetic and not by the bulbo-sacral.—J. C. D.

The pharmacological and colorimetric determination of ADRENALIN in pure and decomposed solutions and ADRENAL extracts (Ueber die pharmakologische und Kolorimetrische Auswertung reiner und zersetzter Adrenalinlösungen sowie von Nebennierenauszügen). Maiweg (H)., Biochem. Ztschr. (Berl.), 1922, **134**, 292-300.

Folin's method for the determination of adrenalin gives too high values for solutions in which the compound is partially decomposed. Very inexact values are apparently given by the colorimetric method when applied to adrenal extracts. The content in adrenalin precursors gives rise to too high values. The pharmacological activity of adrenalin is not enhanced by oxidative decomposition.

—F. S. H.

Parabiosis with special reference to the transplantation and extirpation of the ADRENALS. Mayeda (T.), Keio Igaku, 1922, **2**, No. 7; abst., Jap. Med. World (Tokyo), 1922, **2**, 330.

In successful parabiosis the removal of both adrenals in one of the "twins" does not result fatally. Separation of the parabiotes after 4 weeks may be made without death ensuing in either animal, accessory adrenals having had time to proliferate. Parabiosis of animals of different sex causes little or no change in the gonads.

—R. G. H.

Further data on the effect of SUPRARENAL insufficiency (by removal) in rabbits. Marine (D.) & Baumann (E. J.), J. Metab. Research (Morristown), 1922, **2**, 1-18.

The rabbit was chosen for the experiments because removal of its main suprarenal glands while leaving the small accessory cortical glands intact creates a condition of suprarenal insufficiency which is most desirable. The difficulties encountered in attempts to use other animals are pointed out. Eleven experiments are reported. The rate of heat production was determined before and after the production of adrenal insufficiency. Detailed protocols and tables illustrate the results. Careful histological study of the autopsy material was made. It was found that a prolonged absolute rise in heat production was obtained in 27 of 33 rabbits in which the two main suprarenal glands had been completely removed, and in 6 of 15 rabbits in which these glands were frozen with ethyl chloride. It was concluded that increased thermogenesis is due in part to an increased rate of discharge of the iodin-containing hormone from the thyroid, since thyroidectomy prevents this increased heat production. Infection, trauma, nerve injury, diet and muscular activity,

it was decided, are not essential factors in increased heat production.—I. M.

Further observations on the effect of SUPRARENAL insufficiency (by removal) in THYROIDECTOMIZED rabbits. Marine (D.) and Baumann (E. J.), J. Metab. Research (Morristown), 1922, **2**, 777-802.

Almost total thyroidectomy was performed on rabbits which were then kept under standard conditions until thyroid deficiency was apparent. Epinephrectomy was then performed, with the production of sublethal suprarenal insufficiency. Respiratory exchange measurements, made with the modified Haldane open circuit apparatus at different intervals, indicated the absence of typical increase in heat production observed when the thyroid is present. It is concluded that there exists a thyroid-suprarenal cortex interrelationship which is separate from the thyroid chromophil tissue interrelationship. Evidence is pointed out that sufficient but sublethal suprarenal insufficiency in rabbits and in cats causes a rapid loss of iodine from the thyroid.—I. M.

Case of ADRENAL hemorrhage (Un cas d'hemorrhagie des surrénales). Mihcaux (J.) & Marsset (H.), Bull. et mém. soc. méd. d. hôp. de Par., 1923, **47**, 161-163.

An old man of 74 with profuse diarrhea and general fatigue died suddenly. At autopsy bilateral hemorrhage was found.

—F. S. H.

The influence of PANCREATIC infusion and pancreatic juise on ADRENALIN hyperglycemia. Murohashi (T.), Jikwa Zasshi, 1922, No. 266 (July); abst., Jap. Med. World (Tokyo), 1922, **2**, 330.

The author employed infusions of cattle spleens, and in some cases noted an inhibition of experimental adrenin hyperglycemia; in other cases the infusions proved inactive. Protein-free pancreatic juice, boiled pancreatic infusion of cattle and of dog's pancreas all gave negative results.—R. G. H.

The influence of ADRENIN on the retina (Uber den Einflusz des Adrenalins auf die Netzhaut). Nakamura (B.) & Miyake (R.), Klin. Monatsbl. f. Augenh., 1922, **69**, 258-266; abst., Physiol. Abst. (Lond.), 1923, **7**, 611.

Estimation of ADRENALINE in the blood. Okamoto (K.), J. Bact. (Japan), 1921, No. 315; Jap. Med. World (Tokyo), 1922, **2**, 88.

A modified Suto-Inouye method was used for the estimation of adrenaline in the suprarenal. To get rid of interfering substances, the author treated the serum with absolute alcohol and centrifuged at 3,000 r.p.m. for 20 minutes. He then added more $HgCl_2$ and

less Na acetate. He could demonstrate fairly accurately 0.00005 gm. of adrenaline in 5 cc. of the serum.—Physiol. Abst., **7**, 586.

The action of ADRENALIN on the blood sugar (Die Wirkung des Adrenalins auf den Blutzucker). Petényi (G.) & Lax (H.), Biochem. Ztschr. (Berl.), 1921, **125**, 272-282.

These experiments were done on children and infants. It was found that the preliminary hyperglycemia is followed by hypoglycemia; that the variability of the blood sugar in tetany is greater than normal; that the administration of adrenalin in patients with tetany is followed by a hyperglycemia of lesser degree than normal and that hypoglycemia does not appear.—F. S. H.

An intervening mechanism in the fixation of fat by the ADRENAL gland (Sur un mécanisme intervenant dans la fixation des graisses par la glande cortico-surrénale). Policard (A.) & Tritchkovitch (Juliana), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 960-961.

ADRENALIN in the incoercible vomiting of pregnancy (L'adrénaline dans les vomissements incoercibles de la grossesse). Rathery, Gynéc. (Par.), 1922, **24**, 614-615.

Report of 4 cases. The drug was administered either subcutaneously (1 mg. of the hydrochloride in 250 cc. physiological saline) or by ingestion (1 or 2 mg.) or by lavage (1 mg.) for from 2 to 7 days. The results were immediate; vomiting stopped in 24 to 48 hours; acidosis disappeared in 3 or 4 days and weight increased. Relief was permanent. —F. S. H.

Some effect of EPINEPHRIN on the heart of the common bull-frog (Rana catesbiana). Reed (C. I.) & Smith (Erma), Am. J. Physiol. (Balt.), 1923, **63**, 566-582.—T. C. B.

Effects of ADRENALIN and extracts of PANCREAS and LIVER on blood dextrose. Ross (E. L.) & Davis (L. H.), J. Pharmacol. & Exper. Therap. (Balt.), 1922, **20**, 121-128.

Experiments were conducted on dogs. Intravenous injection of 0.25 cc. of a 1-1000 solution of adrenalin per kilo produced an increase of 62% in the blood sugar at the end of 15 minutes. This fell to 31% at the end of an hour. Fresh pancreatic extract brought about a decrease in four out of five trials. This decrease averaged 23% at the end of 15 minutes and had fallen to 5% after one hour. Pancreas extract injection, followed at once by injection of adrenalin, gave an increase of 39% 15 minutes after the injections. This fell to 9% at the end of one hour. The results obtained from injection of a mixture of the pancreas extract and adrenalin after incubation for 30 minutes were not constant. The injections were controlled by injection of liver extract and of liver extract followed by adrenalin. The extract of liver gave small increases in glycemia, while

extract of liver followed by adrenalin gave a summated increase. These experiments show that adrenalin increases and pancreas decreases glycemia.—G. E. B.

Primary spontaneous tumors of the kidney and ADRENAL in mice. Studies on the incidence and inheritability of spontaneous tumors in mice. Slye (M.), Holmes (H. F.) & Wells (H. G.), J. Cancer Research (Balt.), 1921, **6**, 305-336.

In a series of 33,000 autopsies on mice of the Slye stock dying natural deaths at all ages, there were 4 tumors of the adrenal, namely, 1 cortical adenoma from a misplaced intrarenal adrenal rest, and 3 mesothelial tumors. Of 16 tumors of the kidneys in the same series, one was a hypernephroma. As these tumors occurred in 33,000 mice which presented approximately 5,000 other tumors, it is evident that tumors of these organs are uncommon in mice, or at least in the Slye stock.—J. P. S.

ADRENAL insufficiency [La insuficiencia suprarenal (astenia e intoxicación)]. Soler (F. L.), Semana méd. (Buenos Aires), 1922, **29**, 305-309 (August 10); cit., J. Am. M. Ass. (Chicago), 1922, **79**, 2042.

Experimental studies on the ADRENIN content of the ADRENALS. I. Communication. Takahashi (K.), Hokuetsu Igakkwai Zasshi, 1922, **37**, No. 3 (June); abst., Jap. Med. World (Tokyo), 1922, **2**, 329.

Bleeding causes a sudden decrease of the adrenalin content of both adrenals, which is restored in about 48 hours. Secretion of adrenalin depends upon intact connections with sympathetic ganglia. Nicotin temporarily augments the adrenalin secretion, but afterwards inhibits it. Electrical stimulation of the visceral nerves temporarily augments the adrenalin secretion. Electrical stimulation of the vagus is without effect on adrenalin secretion. Also atropin has no influence.—R. G. H.

(ADRENIN) Is asphyxia the cause of drug hyperglycemias? Tatum (A. L.) & Atkinson (A. J.), J. Biol. Chem. (Balt.), 1922, **54**, 331-350.

Various studies of the blood sugar and the alkaline reserve of the blood of rabbits treated with drugs were reported. It was demonstrated that cyanide and carbon monoxide produce a much greater fall in reserve and much less sugar rise than adrenin or ether. Since the fall in reserve is probably caused by diminished oxidization, the hyperglycemia caused by the drugs cannot in each case be due to diminished intracellular oxidation. The fall in reserve should be a measure of the same diminution of oxidation, and this same diminution of oxidation should lead to a relatively definite glycogenolysis. There is absolutely no available evidence of any contributary action of asphyxia in adrenin hyperglycemia.—F. S. H.

(ADRENALS) Pubertas precox and fragilitas osseum. Weil, Klin. Wchnschr. (Berl.), 1922, **1**, 2114-2115.

Demonstration of a girl who, at 9 months, had complete development of the breasts. When she was 1½ years of age menstruation began. The sexual organs were developed as in a girl of 15. The author considers this as due to precocious development of the adrenal system. When she was 1½ she had her first bone fracture. After that she had 7 fractures. The sclerae showed a trace of blue color.—J. K.

A note on ADRENALINE therapy. Worcester (A.) & O'Hara (D.), Boston M. & S. J., 1923, **188**, 58-59.

A case report.—J. C. D.

Hyperplasia of the ADRENAL cortex [Sull' iperplasia della corticale surrenale (osservazione anatomo-patologica e considerazioni cliniche)]. Zalla (M.), Riv. di. patol, nerv. (Firenze), 1922, **27**, 485-492.

The case is described of a woman 58 years old, in good health until 12 years of age, when she had typhoid fever, followed by slight epileptic attacks. Menstruation stopped when she was about 20. Although she had been lively and intelligent, she gradually developed psychophysical retardation. She continued to have almost regularly once a month epileptic fits, followed by confusion and auditory hallucination. She died of bronchopneumonia. At autopsy the two adrenal glands appeared to be of abnormal size (the right 13 gm., the left 20 gm.) The volume was due to the increased size of the cortex—uniform and diffuse; with the exception of the frequent vacuolation of the protoplasm, the cells did not present other abnormality.—G. V.

The production of DIABETIC lipemia in animals, and observations on some possible etiologic factors. Allen (F. M.), J. Metab. Research (Morristown), 1922, **2**, 219-298.

A fairly extensive review of the literature on fat metabolism and brief extracts of 377 references are given. Dogs made diabetic by partial removal of the **pancreas** were used. The "positive" etiologic influences tested were: active diabetic symptoms, diet, and individual idiosyncrasy. The "negative" etiological influences tested were: direct endocrine influence of the pancreas; liver deficiency; **adrenal** deficiency; **thyroid** deficiency and overactivity; **sex gland** deficiency; variation in species; age; degree of hyperglycemia and glycosuria; acidosis; alkali administration; diet; administration of cholesterol and lecithin; differences in nutritive state; anemia; exercise; vitamines; levulose and phlorizin. It was found that there is a complete similarity between clinical and experimental diabetes in regard to lipemia. Each specimen of blood was analyzed in three

parts—whole blood, plasma and corpuscles—for total fat, lecithin and cholesterol. Apart from a sufficient supply of fat in the diet, the one indispensable prerequisite for diabetic lipemia was found to be the existence of active severe symptoms in the form of glycosuria and hyperglycemia. Mild cases with high glycosuria and severe cases with glycosuria abolished by diet were found never to exhibit extreme lipemia, however high the fat intake. It was concluded that diabetic lipemia represents some secondary breakdown in fat metabolism, not directly connected with the endocrine function of the pancreas and not due merely to excess of fat in metabolism or loss of sugar in the urine. It was found that there are wide individual variations in susceptibility to lipemia. Tests under all of the endocrine, dietary, drug and other influences listed failed to reveal the exact nature of the disturbance or the origin of susceptibility to lipemia.—I. M.

Observations on the progressiveness of DIABETES. Allen (F. M.), Med. Clin. N. Am. (Phila.), 1922, **6**, 465-474.

This is an important discourse dealing with probable causal relationships upon which the course and prognosis of diabetes mellitus depend. The avoidance not only of glycosuria but of hyperglycemia is the means of curbing the downward progress of the patient. The function of the islands of Langerhans is impaired by infection and intoxication; this leads to the usual diabetic symptoms, rendering the pancreas highly susceptible to functional overstrain. Case histories exemplify the contrast between patients treated with a diet restricted to overcome functional strain and those treated with a high diet in the fallacious attempt to "build up" the patient. There appears to be no mysterious element to account for the progressiveness of diabetes mellitus, but only infections and functional overstrain. It is urged that in the physical examination of students in schools and colleges, urinalysis be included in order promptly to detect and treat early cases of the disease. Moreover, since there is no valid distinction between true diabetes and other forms of glycosuria with hyperglycemia, even the mildest cases of the former are susceptible to aggravation from functional overstrain.—I. B.

Present status of DIABETIC treatment. Allen (F. M.), N. Jersey M. Soc. J. (Orange), 1923, **30**, 1-15; cit., J. Am. M. Ass. (Chicago), 1923, **80**, 657.

Changes in the chemical composition of the blood in health and DIABETES after ingestion of salt solutions (Uber Aenderungen der chemischen Zusammensetzung des Blutes nach dem Trinken von Salzlösungen bei Stoffwechselgesunden und Zuckerkranken). Arnoldi (W.) & Ettinger (S.), Klin. Wchnschr. (Berl.), 1922, **1**, 2082-2083.

The authors studied the effect of warm water, solutions of Karlsbad salt, Na_2SO_4, citrate of sodium and bicarbonate of sodium on the blood sugar, the amount of NaCl and proteins in the blood, and the alveolar CO_2 tension in arterial blood. The blood sugar usually showed a decrease, which was much more marked in diabetes than in health. NaCl change was not constant; normal persons generally showed an increase, while diabetics usually showed a decrease. The CO_2 tension and the protein content of the serum were in nearly all cases lowered.—J. K.

Some chemical reactions of INSULIN. Best (C. H.) & Macleod (J. J. R.), J. Biol. Chem. (Balt.), 1923, **55**, xxix-xxx; see also, Am. J. Physiol. (Balt.), 1923, **63**, 390 (Proc.).

Insulin from pancreas of ox or pig gives the usual protein reactions. That from the skate does not. The former is due to protein impurities. Insulin does not give the usual color reactions for **epinephrin.** Moderate heat does not affect the reactivity in faintly acid reaction. Moderate alkalinity is also harmless for short periods. Insulin in acid is adsorbed by charcoal, etc. Insulin apparently does not dialyze and is weakened by the dialyzer. The potency of insulin preparations may be weakened by passing through a Berkfeld filter.—F. S. H.

Influence of certain carbohydrate diets on glycemia in man, normal or DIABETIC (Influence de certains aliments hydrocarbonés sur la glycemie de l'homme normal ou diabétique). Bonorino Udaondo (C.) & Casteigts (M.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 392-393.—T. C. B.

DIABETIC gangrene of the scrotum and integuments of the penis: antigangrenous serotherapy: cure (Gangrène diabétique du scrotum et des téguments de la verge. Serothérapie antigangreneuse. Guérison). Chauffard (A.), Huber (J.) and Marquézy (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1922, **46**, 270-273.

The influence of PANCREATIC perfusates on the blood sugar, D:N ratio and respiratory quotient of depancreatized animals. Clough (H. D.), Stokes (A. M.), Gibbs (C. B. F.), Stone (N. C.) & Murlin (J. R.), J. Biol. Chem. (Balt.), 1923, **55**, xxx-xxxi.

Perfusion of the pancreas of the dog, pig and cow, by Clarke's method, withdraws the antidiabetic substance in sufficient concentration to affect favorably all the major symptoms of diabetes produced by depancreatization. In several instances the blood sugar was reduced to normal or lower by a single injection; the excretion of sugar was stopped by 2 or 3 injections. When the perfusion fluid is made slightly acid more potent extracts are obtained. The name glucopyron is suggested for the effective extracts obtained from the pancreas.—F. S. H.

The occurrence of ketone bodies in the urine of normal rabbits in a condition of hypoglycemia following the adminstration of INSULIN—a condition of acute acidosis experimentally produced. Collip (J. B.), J. Biol. Chem. (Balt.), 1923, **55**, xxxviii-xxxix.

While we have in insulin a substance which will correct all the acidotic signs, both in experimental animals rendered diabetic and in patients suffering from diabetes (if the dosage is adequate), it will nevertheless produce many of the cardinal symptoms of acidosis when administered to normal animals in amount sufficient to produce hypoglycemia of a marked degree.—F. S. H.

The demonstration of an insulin-like substance in the tissues of the clam (Mya arenaria). Collip (J. B.), J. Biol. Chem. (Balt.), 1923, **55**, xxxix.

Since insulin aids in the storage of glycogen in the dog, it might be expected that wherever glycogen occurs there would be insulin. A substance acting somewhat similar to insulin was extracted from the tissues of the clam.—F. S. H.

The original method as used for the isolation of INSULIN in semi-pure form for the treatment of the first clinical cases. Collip (J. B.), J. Biol. Chem. (Balt.), 1923, **55**, xl-xli.

Of great historical interest.—F. S. H.

Delayed manifestations of the physiological effects of INSULIN following the administration of certain pancreatic extracts. Collip (J. B.), Am. J. Physiol. (Balt.), 1923, **63**, 391-392 (Proc.).

Certain extracts produce no immediate hypoglycemia. One to four days after inoculation, however, animals may show hypoglycemia. It would seem that insulin does not exist as such in any quantity in the islet cells. The potency of the extract is due to the method of extraction used, and suggests that a mother substance is activated by certain reagents. In delayed action the mother substance is present and is gradually activated after injection.—T. C. B.

DIABETE et acidose. Desgrez (A.), Bierry (H.) & Rathery (F.), Compt. rend. Soc. de biol. (Par.), 1922, **86**, 245-247.

These authors take the view that in certain conditions metabolic disturbances can only be avoided by a definite relationship in the amounts of protein, fat and carbohydrate in the diet. They have investigated the diabetic from this point of view. They divide diabetics into: (1) those who eliminate acetone bodies regularly in large amounts; (2) those who eliminate them intermittently; and (3) those whose urinary N is high. A determination is first made of the sugar and acetone bodies excreted after 2 days in which only water is taken. They find that for each patient a diet can be determined containing protein, fat and carbohydrate in a ratio peculiar

for the patient, on which the excretion of acetone bodies is as low as when fasting.—Physiol. Abst., **7**, 121.

DIABETIC acidosis. Desgrez (A.), Bierry (H.) & Rathery (F.), Bull. Acad. de méd. (Par.), 1923, **89**, 25-33; abst., J. Am. M. Ass. (Chicago), 1923, **80**, 805.

Some properties of an active constituent of the PANCREAS (INSULIN). Doisy (E. A.), Somogyi (M.) & Shaffer (P. A.), J. Biol. Chem. (Balt.), 1923, **55**, xxxi-xxxii.

Insulin has been prepared by methods of Collip, Banting and Best. Purification reached the point in which about 0.25 mg. of material produced hypoglycemia in rabbits of 1 kilo weight. It is a white powder containing 14% nitrogen. It is free from phosphorus. It gives a distinct biuret test. Its solutions are levorotary. It is acid resistant. It is soluble in water except at cH 5-6. It is fairly soluble in alcohol. It is pretty well precipitated by half saturated ammonium sulfate. It appears to be an albumose or globulin. The identity is not established. The method of preparation is given.—F. S. H.

Experimental DIABETE gras. Friedman (G. A.) & Gottesman (J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, 210-212.

In 8 dogs the authors demonstrated that diabetes with obesity can be produced: (1) "by almost complete **thyroidectomy** in partially **depancreatized** dogs," and (2) "by ligation of one pancreatic duct."—J. C. D.

Influence on the respiratory metabolism of PANCREATIC extract administered by mouth to depancreatized dogs. Gibbs (C. B. E.) & Murlin (J. R.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 198.

There was an elevation of the respiratory quotient when measured 2 to 4 hours after such administration. The methods of preparation and the tabulated result of one experiment are included.
—J. C. D.

An atypical adenoma of the PANCREAS originating in islet tissue. Goldblatt (H.), J. Cancer Research (Balt.), 1921, **6**, 277-283.

Report of a case the pathology of which is sufficiently described in the title. There was no apparent disturbance of carbohydrate metabolism.—J. P. S.

Plea for testing selected single specimens of urine, with special regard to DIABETES. Gray (H.), Boston M. & S. J., 1923, **188**, 168; abst., J. Am. M. Ass. (Chicago), 1923, **80**, 800.

The effect of Eck's fistula upon PANCREATIC DIABETES in dogs. Hendrix (B. M.) & Sweet (J. E.), J. Biol. Chem. (Balt.), 1923, **55**, 161-169.

It has been shown that glucose practically disappears from the urine of Eck's fistula pancreatectomized dogs after they have fasted for several days. There is, however, definite hyperglycemia in such animals even after prolonged fasting. The alkali reserve in the blood of these dogs does not decrease so rapidly as after simple pancreatectomy and the ability to utilize sugar is very slight. It is suggested that little glucose is formed from amino-acids in Eck's fistula dogs.—F. S. H.

DIABETES MELLITUS. Herndon (R. F.), Illinois M. J. (Oak Park), 1923, **43**, 137-144.

A good survey of the etiology and treatment of diabetes mellitus The importance of diet in treatment is emphasized.—I. B.

Observations in DIABETES (Beobachtungen bei Diabetes). Höpfner (H.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1284-1285.

In diabetes exposure of the liver to x-rays did not change the blood sugar; x-ray treatment of the **adrenals** first produced a rise of the blood sugar, followed by a temporary fall. When bone marrow was exposed to x-rays no influence on sugar in the blood or urine was seen. Administration of **antithyroidin** in diabetes had no influence upon the glycosuria. Bone charcoal or bolus alba did not change the glycosuria nor produce an increase in the quantity of sugar, acetone and diacetic acid in the urine.—J. K.

(PANCREAS) The islands of Langerhans in the skate. Jackson (S.), J. Metab. Research (Morristown), 1922, **2**, 141-147.

By the use of Lane's method for identifying islet tissue with Bensley's neutral gentian stain for differentiation of alpha and beta cells, the author has studied the structure of the pancreatic tissue in the skate. The islets stand out as less deeply stained areas surrounding the pancreatic ducts. In each islet there are seen the larger alpha cells with deeply staining granules and the more numerous smaller beta cells, the cytoplasm of which is clear. No definite "transitional cells" were seen, a fact which makes it improbable that acinar cells are converted into islet cells as has been claimed.—I. M.

(DIABETES) The interpretation of blood sugar estimations that are near the normal. John (H. J.), J. Lab. & Clin. M. (St. Louis), 1922, **8**, 145-152.

The author points out in a series of cases that we cannot regard a blood sugar level which is near the normal as normal unless we know under what conditions it was obtained (i. e., whether the subject is on a diet or has been eating sparingly for a time) and unless we can demonstrate by a glucose tolerance test that the slight rise is of nondiabetic origin. Border-line cases are the most difficult to diagnose and yet the most interesting and important. When

it is seen that the border-line subject has a diabetic trend, a simple restriction of carbohydrates will carry him through life comfortably. Usually the total calories need not be changed. On the other hand, if such a case is allowed to drift along without dietary supervision, he will reach the stage of diabetes when a marked restriction of proteins and total calories, as well as carbohydrates, will be necessary.—I. B.

(DIABETES) The excretion of sugar in the urine in health and disease. Kast (L.), Croll (Hilda M.) & Myers (V. C.), J. Lab. & Clin. M. (St. Louis), 1923, **8**, 227-241.

In a comparative study of different methods for the determination of sugar in normal urine, the authors conclude that by the method of Benedict and Osterberg there is shown to be an increase in the amount of reducing sugar excreted hourly after meals. A diet rich in carbohydrates produces an increase in the sugar excreted, as compared to a low carbohydrate diet. In the 152 cases studied, there were no marked variations from the normal sugar excretion on ordinary diets, except in cases of diabetes mellitus. Moreover, when by dietary regulation the urine is rendered "sugar free," the daily amount of sugar excreted is practically normal. —I. B.

New ideas on, and treatment of, DIABETES MELLITUS (Neue Auffassung und Behandlung des Diabetes mellitus). Klieneberger (C.), Klin. Wchnschr. (Berl.), 1922, **1**, 1630.

The war brought out the fact that traumatic diabetes is very rare. Excretion of sugar after infectious diseases is not so rare. There is danger of protein over-feeding. The author believes that individualized treatment is necessary, but that the severe therapy advocated by Geulpa or Allen is unsatisfactory.—J. K.

Soya bean flour in treatment of DIABETES MELLITUS. Jones (C. B.), Med. Sentinel (Portland, Ore.), 1921, **29**, 422-424.

Jones believes that soya beans tend to eliminate the craving for carbohydrate in the diabetic subject and to provide a non-carbohydrate food of great value.—M. B. G.

Examination and medical surveillance of the DIABETIC (Examen et surveillance médicale d'un diabétique). Labbé (M.) & Bith (H.), J. de méd. de Par., 1921, **40**, 349-350.

Further experiments with high fat diets in DIABETES. Leclercq (F. S.), J. Metab. Research (Morristown), 1922, **2**, 39-55.

Three cases of diabetes are reported in full which confirm the author's previous conclusions that high fat diets are harmful in that they overstrain the function of the carbohydrate mechanism as well as cause ketonuria. The value of undernutrition by diets which keep the blood sugar near the normal level is emphasized.—I. M.

Experiments on the mechanism of the action of INSULIN. McCormick (N. A.), Macleod (J. J. R.), O'Brien (K.) & Noble (E. C.), Am. J. Physiol. (Balt.), 1923, **63**, 389-390 (Proc.).

Insulin enters the tissue cells and creates a vacuum for glucose, as a result of which sugar is withdrawn from the blood more quickly than the liver and muscles can supply it. The vacuum may be due to polymerization of glucose within the cell. Restoration may occur in deglycogenated animals, showing that a process of gluconeogenesis has been set up.—T. C. B.

The source of INSULIN. A study of the effect produced on blood sugar by extracts of the PANCREAS and principal islets of fishes. Macleod (J. J. R.), J. Metab. Research (Morristown), 1922, **2**, 149-172.

A report on the effect of pancreatic extracts of various fish on carbohydrate metabolism, especially in regard to their effect on the blood sugar in rabbits. Extracts were prepared from the pancreas of representative Elasmobranchii (dog fish and skate), from the principal islets of representative Teleostei (sculpin and angler fish) and from the zymogenous (acinar) pancreatic tissue, as free as possible from islets in Teleostei. Such extracts were prepared according to the method employed by Banting and Best for obtaining insulin from the mammalian pancreas, i. e., by alcohol extraction at low temperatures. Blood sugar determinations were made in a series of rabbits, both before and at intervals after administration of the extracts. It was found that very potent preparations of insulin can be obtained from this source, except that none could be obtained from the acinar pancreatic tissue of the bony fish. This offers additional proof of the insular origin of insulin and suggests a probably significant source for insulin.—I. M.

The influence of alkali therapy on ketosis in DIABETES MELLITUS. Mosenthal (H. O.) & Killian (J. A.), J. Biol. Chem. (Balt.), 1923, **55**, xliii.

Six patients were given a standard diet of 30 gm. carbohydrate, 130 gm. fat and 40 gm. of protein, giving 1,400 to 1,500 calories. Sodium bicarbonate was given by mouth in 30 to 45 gm. doses per day for a time. A decrease in the blood acetone and sugar was found associated with a rise in the carbon-dioxide combining power. Urinary sugar decreased. The effect persisted in some cases for 10 days.—F. S. H.

Maintenance by diet in the treatment of DIABETES MELLITUS. Mosenthal (H. O.), Med. Clin. N. Am. (Phila.), 1922, **6**, 403-614.

The author urges conservation in the rigidity and duration of dietary restriction, lest the patient, though sugar free, lapse into a dangerous state of inanition. There are times when the conventional criteria of blood and urine sugar must be boldly, though

cautiously, overstepped. Complete elimination of sugar from the urine and blood may be accomplished in most patients without recourse to starvation. Mosenthal presents the following patients rendered normal as to glycemia and glycosuria: 18 on a protein fat diet taken as desired; 8 on a protein fat diet of 1,000 to 1,500 calories; 3 on a protein fat diet of 500 to 1,000 calories; 4 by starvation. Under the above dietary scheme the patients are kept upon an unrestricted protein fat diet or upon a 1,500 calorie diet of protein and fat until the sugar in the urine ceases to diminish. If it does not entirely disappear, then progressively increased food restrictions are ordered until normal is attained. The most important advantage of this conservative procedure is that the nutrition, health and strength of the patient are conserved as far as possible. By these means a certain reserve is provided in case the disease becomes unmanageable and more vigorous food restrictions prove to be necessary. Though there are certain broad principles upon which all these patients are to be treated, individualization is important.—I. B.

The influence of PANCREATIC extracts without the aid of alkali upon the metabolism of the depancreatized animal. Murlin (J. R.), Kramer (B.) & Sweet (J. E.), J. Metab. Research (Morristown), 1922, **2**, 19-27.

The authors report that in totally depancreatized dogs saline extract of ox pancreas given subcutaneously caused marked diminution in the blood sugar and in the excretion of glucose. **Thyroidectomy** did not alter in any way the activity of carbohydrates in these animals, thus proving that the increase in the respiratory quotient following injection of pancreatic extract was not due to thyroid activity.—I. M.

Surgical aspects of DIABETES. Murphy (J. P.), Long Island M. J. (Brooklyn), 1921, **15**, 224.

Surgical cases can be divided into two groups: (a) diabetes is the essential disease and the surgical lesion is the accident, such as carbuncle in a diabetic; (b) surgical lesion is the essential feature and diabetes the accident, such as acute appendicitis in unsuspected diabetes. In the first type, operation is of election, while in the second it is of necessity and the diabetes should be disregarded. —M. B. G.

DIABETES during pregnancy (Diabetes en el embarazo). Perez (M. L.), Semana méd. (Buenos Aires), 1922, **29**, 393-398 (August).

Report of a woman of 23 years in whom typical diabetes developed late in pregnancy. This disappeared after the birth of the child.—B. A. H.

Physical measurements of DIABETIC patients. Root (H. F.) & Miles (W. R.), J. Metab. Research (Morristown), 1922, **2**, 173-197.

From a study of 133 diabetic patients the authors found that although normal in stature the subjects had been on the average 20% overweight prior to onset and were about 10% underweight at the time of examination. The 56 women showed more severe diabetes and lower carbohydrate tolerance than the 77 men observed. The older patients had been more obese and had lost a larger percentage of their weight. The type of diabetics who apparently had never been overweight had the narrow type of chest and probably had been fat for their build. Obesity was found to be closely related to the onset of diabetes mellitus, but the intensity of the disease frequently appeared to be inversely proportional to the amount of excess fat. Chest circumference was not found to be a satisfactory measure for predicting normal weight. Vital capacity may be as great in diabetic as in normal subjects and is, therefore, not of any help in uncomplicated diabetes.—I. M.

Normal, DIABETIC and Basedowian alimentary hyperglycemia (Blood sugar studies) [Die alimentäre Hyperglykämie bei Gesunden, Diabetikern und Basedowischen (Blutzuckerstudien)]. Rosenberg (M.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1922, **93**, 208-240.

Experiments with 100 gm. dextrose dissolved in 300 cc. caffeinless coffee substitute, which was given 2 hours after the first breakfast. The blood sugar was examined first on the empty stomach and thereafter at about half-hour intervals for 2 hours. Duration of intestinal resorption may be considered as constant and has no important influence upon the blood sugar curve. The sudden rise of the blood sugar curve may be caused by decreased carbohydrate assimilation in the liver or by increased consumption. The duration of hyperglycemia depends not only on the duration of influx from the liver, but also on the amount of sugar absorbed by the muscles. The curve usually reaches a maximum in normal subjects ½ hour after excretion of the dextrose. The increase averages 0.1%. After 2 hours the blood sugar is usually normal. In diabetics hyperglycemia is increased, continues longer, and reaches the maximum later than in normal subjects. The author especially emphasizes this last fact; he finds a certain parallelism between the gravity of the diabetes and the time the maximum is reached. Most diabetics reach the maximum in 1.5 to 2 hours. The author believes that in diabetes the liver forms sugar more easily, the sugar forming activity being greatest shortly after ingestion because its stimulating effect is gradually increasing. He states that possibly the ability to form glycogen in the tissues, especially in the muscles, diminishes simultaneously. Three cases of renal diabetes

showed a normal hyperglycemia curve after dextrose ingestion, but measurable sugar in the urine. In case of Graves' disease the curves are not regular—in several cases being normal, in others resembling the diabetic curve. The pathological alteration of the curve is not parallel to the gravity of clinical symptoms of **hyperthyroidism.** Sugar excretion from the liver seems to be increased in these subjects also.—A. B.

(DIABETES) The progress of potentially DIABETIC persons in relation to dietary control. Sherrill (J. W.), Med. Clin. N. Am. (Phila.), 1922, **6**, 719-737.

A report of the result of the treatment of a series of cases of supposed latent or potential diabetes. It is pointed out that tolerance is decreased with prolonged overnutrition and gradual rise in body weight. On the other hand, persons with proved tendency to lowered glucose tolerance, but without frank diabetic manifestations, improve in carbohydrate assimilation following application of the principle of low nutrition.—I. B.

Balancing the DIABETIC diet. Strouse (S.), J. Am. M. Ass. (Chicago), 1922, **79**, 1899-1900.

A line of treatment for diabetes which seeks to avoid the starvation methods of Allen and Graham is that in which a proper proportion of fat is administered. This paper gives rules for determining quickly the right amounts of protein, fat, and carbohydrate appropriate to a given case. The basal metabolism is first determined, and the total caloric value of the food should approximate to this. The protein should be the minimum amount compatible with nitrogen equilibrium, which is given as 0.66 gm. per kilo of body weight. The carbohydrate content should be that amount which can be tolerated (this to be determined during 2 days on a fixed diet; it is the intake less the amount in the urine), subtracting from this tolerated amount 58% of the protein. The rest of the caloric requirement should be fat, though this must be within limits 2.5-4.0 times the available carbohydrates, otherwise there will be ketonuria.—Physiol. Abst., **7**, 610.

Dinitrosalicylic acid; A reagent for the estimation of sugar in normal and DIABETIC urine. Sumner (J. B.), J. Biol. Chem. (Balt.), 1921, **47**, 5-9.

A new colorimetric method.—F. S. H.

DIABETES in old age (Contribution à l'étude du diabète sucré chez le gens âgés. Yeanty (A. y R.), Thèse pour le Doctorat en Médecine, Bordeaux, 1922.

Diabetes is rarely seen in a subject over 60 years of age. In an old person the symptoms are weakened. Nutritional disorders,

albuminuria, rheumatism, gout, asthma, obesity, and eczema are often associated with diabetes.—E. G.

Post-traumatic calcification of the PANCREAS, with DIABETES. Wells (H. G.), Tr. Chicago Path. Soc., 1922, xi, 255-256; in full, Am. J. Med. Sc. (Phila.), 1922, **164**, 474-492.

This report concerns a "previously healthy young man who fell from a wagon and was probably run over by at least one of the wheels. He received fractures of several ribs on the left side, traumatic infarction of the left **adrenal**, the upper pole of the **spleen**, and the entire left kidney, together with a crushing injury of the pancreas which resulted in complete destruction of the secreting elements, which were replaced by a large quantity of dense fibrous tissue and extensive deposits of calcium salts." The urine in the bladder at necropsy contained sugar. "A review of the literature has failed to reveal a similar case of extensive pancreatic calcification, or an analogous case of diabetes following crushing injury of the pancreas."—J. P. S.

Disseminated sclerosis as a cause of myopia and DIABETES (La esclerosis diseminada como causa de la miopia deletera y de la diabetes). Wernicke (O.), Semana méd. (Buenos Aires), 1921, **28**, 97-105.

The author believes that specific spirochetosis produces sclerosis "en plaques," retinal detachment, severe myopia, chronic rheumatism, serious incretory disorders and diabetes.—B. A. H.

Analyses of blood lipoids in DIABETIC animals and patients. Wishart (M. B.), J. Metab. Research (Morristown), 1922, **2**, 199-217.

A partial report of an extensive study on lipemia. Careful observations on the cholesterol, lecithin, total fat, fatty acids, glycerids, blood and urine sugar and acetone and plasma CO_2 were made in diabetic dogs and patients under varying conditions. Diets were varied as regards the relative proportions of fat, protein, carbohydrate, alcohol and total caloric value. Observations were made before and at intervals after ingestion of cholesterol and lecithin. It was found that marked lipemia is due chiefly to increase in neutral fat. The higher the degree of lipemia, the higher is the ratio of glycerids to other lipoids such as lecithin and cholesterol. Total fats may be very high with a clear plasma, and marked turbidity may be present without marked hyperlipemia. Some degree of lipemia may persist long after hyperglycemia, glycosuria and acidosis have disappeared in severe cases. Cholesterol or lecithin feeding have no decisive influence in either producing or clearing up lipemia. No uniform parallelism was observed between the sugar or acetone in blood or urine and the accompanying degree of lipemia.—I. M.

Microphotographs of a case of DIABETES INSIPIDUS. Lewy (F. H.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1663.

Demonstrations of microphotographs, proving that diabetes insipidus is due to changes in the ganglion parahypophysis, situated in the tuber cinereum.—J. K.

Case of DIABETES INSIPIDUS successfully treated by PITUITARY extract. Reece, J. Missouri M. Ass. (St. Louis), 1921, **18**, 463.

When admitted to the metabolism ward the patient's fluid intake and output ranged from 12 to 15 liters and could not be reduced below 7 liters. **Adrenalin** by mouth and duodenal tube was without effect. Desiccated pituitary extract, posterior lobe, was given by mouth in salol-covered capsules, the dose being ½ gr., t. i. d. at first, and increasing gradually to 4 gr. four times a day. Intramuscular injection of pituitary fluid was also effective, but desiccated extract in powder form was not successful when given by mouth or rectum.—M. M. H.

Neurologic phase of ENDOCRINOLOGY. Bitler (C. C.), Indiana State M. Ass. J. (Ft. Wayne), 1922, **15**, 414-423.

See Endocrin., **7**, 130.

(ENDOCRINE) The character and the cause of Paget's osteitis deformans (Zur Frage des Wesens und der Pathogenese der Ostitis deformans Paget). Caan (P.), Beitr. z. klin. Chir. (Tübing.), 1922, **125**, 212-244.

This is considered by some investigators as an endocrine disease and many cases are reported in which changes in the endocrine organs have been found at autopsy. Askanazy found pathological changes in the **thyroid**; Meyer and Schmorl found very large **parathyroids**; in a case of Recklinghausen's disease there was a basophil adenoma of the **hypophysis** without other symptoms. Caan advances a new theory as follows. The disease begins with endocrine disturbances; pathological hormones are produced and cause inflammation of the bone marrow, followed by hyperplasia and hemorrhages. Heredity predisposition probably has a rôle. In some cases organotherapy is reported to have been unsuccessful; in others, thyroid extract seemed to bring about good results.—J. K.

Stiffness of the vertebral column and ENDOCRINE disturbance (Wirbelsäulenversteifung und Störungen der innere Sekretion). Cohn-Wolpe (C.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1505-1507.

Report of a case. The vertebral column was exceedingly stiff. There were also very marked symptoms of **thyrogenous** origin (exophthalmus; positive Moebius, Stellwag and Grafe symptoms; no goiter). The skin of the trunk, and especially in the axillae and groins, showed dark pigmentation. The mucous membrane, how-

ever, was not pigmented. A few references from the literature concerning diseases of the joints and endocrine symptoms are quoted. The author discusses whether the patient suffered from Addison's disease, but the symptoms which would be of special importance, such as blood pressure, sugar tolerance and ergographic findings, are not mentioned.—J. K.

(ENDOCRINE) Sclerodermic dystrophy (Ueber sklerodermische Dystrophien). Curschmann (H.), Med. Klin. (Berl.), 1921, **17**; 1223-1225; abst., Schweiz. med. Wchnschr. (Basel), 1923, **53**, 132.

A 42 year old emaciated invalid showed, along with sclerodactilia, **thyroid** deficiency, impotence, marked pigmentation, adynamia, hypotonia and eosinophilia. The author believes that this indicates that pluriglandular insufficiency is the etiologic factor. He includes the skin among the incretory organs involved.—R. G. H.

Diagnosis of disorders of the DUCTLESS GLANDS. Engelbach (W.), Northwest Med. (Seattle), 1922, **21**, 348-351.

Brief report of a lecture, elaborately illustrated by lantern slides, of patients showing striking examples of various types of endocrine diseases.—H. L.

Pluriglandular ENDOCRINE insufficiency (Beitrag zur Klinik der pluriglandulären endokrinen Insuffizienz). Frisch (A.), Med. Klin. (Berl.), 1921, **17**, 1021-1023; abst., Schweiz. med. Wchnschr. (Basel), 1923, **53**, 126.

A case report—interesting in that the beginning of the disorder coincided with a febrile disease.—R. G. H.

Surgical aspects of ENDOCRINOLOGY. Gatch (W. D.), Indiana State M. Ass. J. (Ft. Wayne), 1922, **15**, 423-430.

See Endocrin., **7**, 138.

Mental diseases and the ENDOCRINE sympathetic system (Le malattie mentali in rapporto alla patologia dell' a parecchio endocrinosimpatico). Goldstein (L.), Endocrin. e patol. costituz. (Roma), 1922, **1**, 17-36.

Theoretical, applying Pende's conceptions to psychiatry.—G. V.

An investigation of the basal metabolism in unstable conditions of certain ENDOCRINE glands. Hill (H. G.), Quart. J. Med. (Oxford), 1922, **15**, 331-347.

Hill studied the basal metabolism, by the Douglas bag method [as described by Cathcart, J. Roy. Army Med. Corps (Lond.), 1918, **31**, 339] in 33 patients presenting symptoms ascribed to disorders of one or more of the ductless glands. The results of Hill's estimations of basal metabolism in gross disorders of the **thyroid** gland "agree with those of other observers, and indicate the great value

of this method of examination in estimating the degree of glandular activity prevailing at the time of observation." In "gross disorders" of the pituitary gland, Hill found a marked increase of basal metabolism in two out of three cases of acromegaly; a basal metabolic rate of plus 37.7% in one patient with **dyspituitarism**; and in hypopituitarism, rates ranging from —6.7% to —33.3%. These results "have proved of value in the diagnosis and treatment" of conditions associated with derangements of the **hypophysis**. Estimations of the basal metabolism at the physiological epochs of life in subjects, especially women, who show any tendency to thyroid or pituitary instability, "are of great value in confirming any early abnormality, and indicate lines for suitable treatment." Hill considers that he has established the value of basal metabolism estimations in children suffering from nocturnal enuresis. "An indication is obtained as to those likely to derive benefit from treatment with glandular extracts." Most of these patients showed a low metabolic rate, and improved under thyroid extract. In an investigation of patients suffering from phenomena which are apparently due to parasympathetic overexcitability "a group of cases has been isolated showing a subnormal basal metabolic rate." Several of these patients showed nocturnal enuresis. They "benefit greatly from organotherapy."—J. P. S.

(ENDOCRINE) Indisposition and cachexia by x-rays (Ueber Röntgenkaber und Kachexie). Hirsch (H.), Deutsche med. Whcnschr. (Berl.), 1922, **48**, 1646-1647.

The author believes that the disagreeable sensations felt after x-ray treatment are partially related to the endocrine system. Since endocrine gland extract has been administered the disagreeable symptoms are scarcely ever observed, even in subjects exposed to very large doses of x-rays.—J. K.

(ENDOCRINE) Organ weights in albino rats with experimental rickets. Jackson (C. M.) & Carleton (Rachel), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 181.

Fifty-four rats were used. The degree of rickets varied as shown by the skeleton. There was an increase in the weight of the **adrenals**; a decrease in the weight of the **hypophysis** and especially of the **thymus**; and no change in the **spleen, ovaries, testes** and epididymus.—J. C. D.

(ENDOCRINE) Acrodermatitis atrophicans with scleroderma "en plaques." Jadassohn, Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1663-1664.

A short note. Both symptoms are of endocrine origin.—J. K.

(ENDOCRINE.) An isolated disturbance of salt metabolism as a symptom of a disease of the interbrain (Ueber eine isolierte

Störung des Salzstoffwechsels als Symptom einer Erkrankung des Zwischenhirns). Jungmann (P.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1297; see also, Klin. Wchnschr. (Berl.), 1922, **1**, 1546-1548.

A man of 28 without diseases of the heart or kidneys complained of general dropsy with pluriglandular endocrine symptoms. A radiogram of the skull showed important changes in the sella The blood contained much water and a low quantity of NaCl. The excretion of NaCl was very defective. Theocin or **thyroidin** increased the excretion of NaCl; **pituitrin** had no influence. The author believes this disease to be localized in the interbrain. No other details are given.—J. K.

(ENDOCRINE) The principles underlying the treatment of the diarrheas. Kantor (J. L.), Med. Clin. N. Am. (Phila.), 1922, **6**, 569-570.

A general review of treatment of diarrhea, including diarrhea due to Addison's disease and Basedow's disease. The diarrhea of these latter is sudden in onset, the stools are watery and contain mucus and bilirubin, and the attacks may end as abruptly as they come. Treatment is successfully accomplished by rectal injections of 25 to 30 drops of a 1-1000 solution of **adrenalin** chloride in 200 to 300 cc. of water. Such an enema may be repeated several times a day, as adrenalin by intestine produces no systemic effects. One injection, however, is usually sufficient, as no stools are passed from 15 to 24 hours following the treatment. The author quotes Shapiro and Marine, who have had good results from the use of a glycerin extract of suprarenal cortex by mouth in the alleviation of diarrhea and other symptoms of Graves' disease. In the treatment of diarrhea of pancreatic obstruction, the administration of pancreatic extract or of fresh **pancreas** is of service.—I. B.

(ENDOCRINE) A case of mammary adenocarcinoma with peculiar relation to the glands of internal secretion. Klemperer (P.), Tr. Chicago Path. Soc., 1922, **11**, 295-297.

Brief report of adenocarcinoma of the mammary gland with extensive metastases in the bones. Three of the **parathyroid** bodies were normal in size and shape; the left inferior body was replaced by a tumor measuring 30 by 5 by 3 mm., entirely separated from the **thyroid** gland. Histologic examination revealed both chief and eosinophile parathyroid cells. The former were arranged mostly in cords, partly, however, as alveoli. The latter were accumulated in relatively large groups, one group harboring a small cancer metastasis. The fact that the tumor was composed equally of both kinds of normal parathyroid cells indicated that it was a hyperplasia. Klemperer is of the opinion that this hyperplasia was the result of the destruction of bone by the cancer metastases. He doubts, how-

ever, whether this represents a hyperfunction, because the osteoid tissue about the metastases did not show any trace of calcification. There was also a metastasis in the posterior lobe of the **hypophysis** which entirely destroyed this structure. The patient did not show the symptoms of **diabetes insipidus**, a fact which, he thinks, corroborates the view that the neural portion of the hypophysis does not regulate the secretion of urine.—J. P. S.

Questions of metabolism and INTERNAL SECRETIONS during and after pregnacy (Stoffwechselfragen und innere Sekretion in und nach der Schwangerschaft). Knipping (H. W.), Arch. f. Gynäk. (Berl.), 1922, **116**, 520-534.

The contention of Zangemeister that there occurs a terminal physiological weight increase in pregnancy is substantiated. This is accompanied by a typical change in the respiratory metabolism and is considered as due to certain changes in the function of the anterior lobe of the **hypophysis**. Metabolic and clinical studies show to Knipping that the adiposity of the climacteric is of hypophyseal origin rather than due to ovarian involution.—F. S. H.

(ENDOCRINE) Fatal epilepsy in a GOITROUS woman recently OVARIECTOMIZED. HYPOPHYSEAL hemorrhage. (Etat de mal épileptique mortel chez une femme goitreuse récemment ovariectomisée. Hémorragie de l'hypophyse). Marchand (L.) & Adam (E.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, **47**, 168-172.

The patient showed also neuro-muscular asthenia, crises, disturbances of memory, and facial congestion.—F. S. H.

ENDOCRINE therapeutics in osteomalacia (L'endocrinologia nell' osteomalacia agli intenti terapeutici. Marniucci (C. P.), Arch. di ostet. e ginec. (Napoli), 1923, **17**, 26-33.

A review.—R. G. H.

ENDOCRINOLOGY in its medical aspects. McCaskey (G. W.), Indiana State M. Ass. J. (Ft. Wayne), 1922, **15**, 409-414.

See Endocrin., **7**, 143.

(ENDOCRINE) Some points in metabolism usually neglected by the physician. McClendon (J. F.), J. Lab. & Clin. M. (St. Louis), 1922, **8**, 194-196.

Of interest to the laboratory technician and must be read in its entirety to be appreciated.—I. B.

INTERNAL SECRETION and dermal affections. Matsumoto (S.), Hifuka Hitsunyokikwa Zasshi, 1922, **22**, No. 6 (June); cit., Jap. Med. World (Tokyo), 1922, **2**, 333.

(ENDOCRINE) The relation between INTERNAL SECRETION and fat and lipoids occurring in blood. Okada (Y.), Igaku Chyuo Zasshi, 1922, **19**, No. 24 (June); abst., Jap. Med. World (Tokyo), 1922, **2**, 324.

Fatty acid, cholesterin and lecithin of the whole blood, erythrocytes and plasma increase and decrease in parallel with one another. The Europeans have a little higher concentration of these fatty substances than the Japanese. In Basedow's disease, fatty acid and cholesterin contents seem to decrease in the whole blood and plasma. The injection of **thyroid** preparation is followed by a slight augmentation of these substances, due to intoxication, but after internal administration of small doses a decrease due to augmented metabolism would be the result. The increase which is met with after the extirpation of the thyroid may be explained by the derangement of metabolism, and injection of thyroid preparation to the thyroidectomized animal would result in decrease. **Adrenalin** injection results in a remarkable increase of these substances. **Pituitrin** may also bring about a less notable increase. **Genital** gland feeding causes decrease, which may be due to the increased metabolism.—R. G. H.

Hematologic pictures in endocrine syndromes found associated with epilepsy. Patterson (H. A.), Am. J. Psychiat., 1923, **2**, 427-437 (January).

A study of the blood of 123 cases of endocrine disorders in epileptics. Both **hyperthyroid** cases (6) and hypothyroid cases (6) showed a mononucleosis—the hyperthyroid cases showing an increase of the transitional groups. **Hyperpituitary** cases (14) showed lymphocytosis and the hypopituitary cases (85) showed eosinophilia and mononucleosis.—F. H. A.

Demonstration of some ENDOCRINE cases (Demonstration einiger Fälle von endokriner Funktionsstörung). Petschacher, Wien. klin. Wchnschr., 1922, **35**, 749; see also, Klin. Wchnschr. (Berl.), 1922, **1**, 1628.

A demonstration of a eunuchoid of adipose type; a eunuchoid of tall type; twins of 14, having enuresis, a myxedematous habitus, small sexual organs, and swollen spots on the hands and legs; a "forme fruste" of myxedema with normal sexual organs, but without sexual desires and with defective bone formation; and brothers of 4 years, both of whom have goiters, without myxedema, and without sexual desires. In all these cases it is impossible to find the particular organ which causes these symptoms, since all endocrine diseases are pluriglandular.—J. K.

(ENDOCRINE) Constitutional factors in cancer and tuberculosis (De belangrijkheid der constitutie on der oogpunt van kanker en

tuberculose). Torfs (A.), Vlaamsch. geneesk. Tijdschr. (Gent), 1922, **3**, 581-588.

Constitution, which is conditioned by endocrine and sympathetic factors, is important in relation to cancer and tuberculosis. —J. K.

Functional tests in ENDOCRINOLOGY. Ulrich (H. L.) & Rypins (H.), J. Lancet (Minneap.), 1921, **41**, 364-370.

A comment on the value of functional tests in general and their possible value in endocrinology. They conclude that in the opinion of the majority of workers the estimation of the basal metabolic rate is of permanent value as a clinical function test in endocrinology since it is based on well established physiological facts, that the sugar tolerance test is of questionable value because an adequate method for testing this function has not been developed; and that the adrenalin chloride test is an empirical one and should be abandoned as a functional test since it is not based on any established function.—F. C. P.

An attempted ENDOCRINE explanation of vomiting in pregnancy (Versuch einer Erklärung des Wesens des Schwangerschaftserbrechens). von David (M.), Zentralbl. f. Gynäk. (Leipz.), 1922, **46**, 1067-1069.

The disorder is due to foreign (male) protein.—J. K.

(ENDOCRINE) Experimental studies on the value of organotherapy (Experimentelle Untersuchungen über den Wert der Organotherapie). Zondek (B.), Arch. f. Gynäk. (Berl.), 1922, **117**, 19-26.

General discussion of the utility of incretory materials according to the method of preparation. It is concluded that transplantation or the use of chemically unaltered dried glands is the best and that organ extracts are not specific.—F. S. H.

(GONADS) Morphological significance of the endocrine tissue of the TESTICLE of Urodeles (Signification morphologique du tissu glandulaire endocrinien du testicule des Urodèles). Aron (M.), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 332-335.

(GONADS) The determination of the sexual characters in the Urodeles (Sur le déterminisme des caractères sexuels chez les Urodèles). Aron (M.), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 709-712.

The interstitial cells of the GONADS of cattle with especial reference to their embryonic development and significance. Bascom (K. F.), Am. J. Anat. (Phila.), 1923, **31**, 223-259.

A histological study has been made of the gonads of cattle from the early fetal to the adult stage. Evidence has been secured

to support Lillie's belief that the freemartin in cattle is a sterile female born co-twin with a fertile male, and that normal development of the female has been suppressed by predominance of the male hormones. (In twins of cattle the placental vessels are ordinarily in communication.) Bascom describes **interstitial cells** in the **testis** beginning with the 30 mm. stage and at all succeeding stages to adult life. Interstitial cells do not appear in the **ovary** until the fetus has attained a length of 82 mm. By this time ample opportunity has been afforded for secretion of the male hormone to become established and to modify the potentially female gland. It is significant that freemartins as small as 35 mm. have been observed.—W. J. A.

(GONADS) Cytological modification of the interstitial cells of the TESTICLE in birds having a periodic sexual activity (Sur les modifications cytologiques des cellules interstitiels du testicule chez les oiseaux à activité sexuelle périodique). Benoit (J.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 202-205.—T. C. B.

(GONADS) The existence of sympathic glands in the human OVARY and TESTICLE; their relation to the interstitial gland of the testicle (Sur l'existence de glandes sympathicotropes dans l'ovaire et le testicule humains; leur rapports avec la glande interstitielle du testicule). Berger (L.), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 907-909.

(GONADS) The determination of sexual characters in the Tritons (Sur le déterminisme des caractères sexuels chez les Tritons). Champy (C.), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 192-194.

(GONADS) The conditions of genesis and the sexual hormone in the anourous Batrachia (Sur les conditions de la genèse de l'harmozone sexuelle chez les Batraciens anoures). Champy (C.), Compt. rend. Acad. d. sc. (Par.), 1922, **174**, 497-500.

(GONADS) Hypergenitalism and sexual perversion (Hypergénitalisme et perversions sexuelles). Claude (H.) & Borrel, Médecine (Par.), 1923, **4**, 335-336.

A general discussion. The authors believe that cases of sexual perversion are often caused by hypergenitalism. Biological examination for antisocial reactions bring good results.—R. G. H.

(GONADS) Arterial hypertension following OVARIECTOMY (L'hypertension artérielle consécutive à la castration chez la femme). Cotte, Soc. méd. d. hôp. de Lyon, 1922 (November 21); abst., Presse méd. (Par.), 1922, **30**, 1047.

Cotte believes that ovariectomy is very likely to cause persistence of high arterial blood pressure. In 52 patients whose ovaries

were removed for various reasons, 36 showed this at the end of 3 to 6 months. This is not always true, however; increased tension is often seen in subjects having presented slight hypertension before the operation, and in fibromatous cases. In young women, on the other hand, conservation of an ovary usually tends to check hypertension. Sterilization by radium does not cause elevation of the arterial tension.—R. G. H.

GONAD transplantation in man (Ueber Hodentransplantation beim Menschen). Enderlen, Med. Klin. (Berl.), 1921, **17**, 1439-1442; abst., Schweiz. med. Wchnschr. (Basel), 1923, **53**, 131.

Two cases of homioplastic and 2 of heteroplastic transplantation are reported. The grafts were placed in the abdominal musculature. A few weeks later microscopic examination showed complete necrosis of the parenchyma. The author concludes that such grafts are futile.—R. G. H.

(GONADS) Internal secretions of the female sex organs (Weitere Beiträge zur lehre von der inneren Sekretion der weiblichen Sexual organe). Fellner, Arch. f. Gynäk. (Berl.), 1922, **117**, 304.

See Endocrin., **7**, 155.

(GONADS) Vitamine B and the sex glands (Vitamine B et glandes sexuelles). Gotta (H.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 373-375.—T. C. B.

(GONADS) General etiology and pathogenesis of OVARIAN dysplasia and dysfunction (Allgemeine Aetiologie und Pathogenese der Dysplasien und Dysfunktion der Ovarien). Greil, Arch. f. Gynäk. (Berl.), 1922, **117**, 198-203.

General.—F. S. H.

(GONADS) The clinical importance of TESTICLE experiments (Uber die klinische Bedeutung von Hodenexperimenten). Haberland, Klin. Wchnschr. (Berl.), 1922, **1**, 2598.

Homio- and auto-transplantation are never successful in animals, according to Haberland. Every graft soon changes into connective tissue. The center of the graft and finally the peripheral parts are replaced by connective tissue. In the clinical reports showing marvelous results from transplantations, the subjective feelings of the surgeon as well as of the patient can never with certainty be excluded.—J. K.

(GONADS) A case of precocious sexual development. Harvey (W. G.), Irish J. M. Sc. (Dublin), 1923, **5s.**, 550-551.

A girl of 2½ years menstruated regularly and had adult secondary sex characteristics. At autopsy a tumor attached to the kidney was found.—R. G. H.

(GONADS) The influence of pregnancy on vascular tonus (Der Einfluss der Schwangerschaft auf den Gefässtonus). Hinselmann, Arch. f. Gynäk. (Berl.), 1922, **117**, 161-171.

Increased tonus of pregnancy may be due to **placenta** toxins, or optone or more probably to heightened activity of the **adrenals** or **hypophysis**, when it is not of pathological origin.—F. S. H.

(GONADS) The influence of specific hormones on OVARIAN activity (Beeinflussung der Tätigkeit der Ovarien durch innenspezifische Hormone). Kuhn, Monatschr. f. Geburtsch u. Gynäk. (Berl.), 1922, **49**, 128-135.

A comparative study of luteoglandol and ovoglandol showed the former to be more efficacious. Several brief case reports are made of patients with disturbed menstruation.—F. S. H.

The significance of the female GONADS in renal DIABETES (Die Bedeutung der Funktionen der weiblichen Genitalorgane für die renalin Diabetes). Küstner (H.), Arch. f. Gynäk. (Berl.), 1922, **117**, 158-161.

Clinical observation and experiments on animals lead Küstner to the conclusion that the glucosuria during pregnancy and menstruation, and the lowered sugar tolerance during menstruation is a result of a change of ovarian activity.—F. S. H.

(GONADS) The protective tissue of the interstitial gland of the TESTICLE in the boar (La tissue de soutien de la glande interstitielle due testicule chez le sanglier et chez le verrat). Lacoste (A.), J. de méd. de Bordeaux, 1921, **51**, 356.

The interstitial tissue of the testis of these animals is highly developed.—F. S. H.

(GONADS) Organ and radiation therapy in the genital hypofunction and hypoplasia of the female (Organ und Strahlentherapie in ihren Einfluss auf die genitalen Hypofunktionen und Hypoplasien des Weibes). Landecker (A.), Arch. f. Gynäk. (Berl.), 1922, **117**, 376-383.

(GONADS) Supplementary note on twins in cattle. Lillie (F. R.), Biol. Bull. (Woods Hole), 1923, **44**, 47-78.

Additional cases of freemartins are described and the author restates his theory that the freemartin represents a zygotically female individual modified by the hormones from the blood of a male twin. The hormones are transferred from one twin to the other by anastomosis of the fetal circulations. It is pointed out that the interstitial cells of the testis develop early in fetal life, while it is doubtful whether the ovary produces a hormone till after birth. The case is different, therefore, from that of transplantation of gonads in mammals. In the freemartin the testicular hormone acts

before the development of an ovarian hormone and inhibits the growth of the ovary. The limitations of the theory are pointed out. It should not be applied to all cases of hermaphroditism in cattle, nor should it be extended without further investigation to intersexuality in other mammals.—M. M. H.

(GONADS) Further experimental investigations on the hypertrophy of the sexual glands. Lipschütz (A.), Wagner (C.), Tamm (R.) & Bormann (E.), Proc. Roy. Soc. B., **94**, 1922, 83-92.

A report of the results of an experimental study of varying degrees of castration in a series of guinea pigs. These authors found that after the removal of one testicle or one ovary in young animals the remaining gland hypertrophied and in some instances became twice the size of the normal gland, that small ovarian fragments remaining in the body after removal of one whole ovary and part of the second hypertrophied and attained the weight of an entire ovary, that testicular fragments remaining in the body after the removal of one whole testicle and part of the second did not hypertrophy, this lack of hypertrophy not being due to the degeneraton of the seminiferous tubules. Since very small testicular fragments are sufficient for the development of those sex characters which depend upon the internal secretion of the testicle, it follows that the hypertrophy of the seminiferous part of the testicle after unilateral castration is not a compensatory one. The difference between the behavior of an ovarian and testicular fragment seems to be due to the fact that in the ovary the primordial follicles represent a source of hypertrophy, while in the testicle the single tubules can attain only the same climax as those in the normal testicle.—F. C. P.

(GONADS) OVARY and libido (Eierstock und Geschlechtstrieb). Mansfeld (O. P.), Arch. f. Gynäk. (Berl.), 1922, **117**, 294-298.

(GONADS) Atrophy of the TESTICLES from nervous lesions (Atrophie testiculaire par lésions nerveuses). Marconi (P.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 356-358.—T. C. B.

(GONADS) The relation of anomalies of follicle and CORPUS LUTEUM formation to uterine anomalies (Die Anomalien der Follikel-und Corpus-luteum-Bildung in Zussammenhang mit den Uterus anomalien). Meyer (R.), Ztschr. f. Geburtsch. u. Gynäk. (Stutt.), 1920, **83**, 842-843.

(GONADS) The so-called CORPUS LUTEUM persistans in the light of hidden pregnancy [Die sogenannte Corpus-luteum-Persistenz in Lichte einer verborgenen order Scheinschwangerschaft (okkulte oder Similigravidität)]. Meyer (R.), Ztschr. f. Geburtsch u. Gynäk. (Stutt.), 1920, **83**, 843-844.

Speculation.—F. S. H.

(GONADS) The lipoids of the human OVARY (Ueber die Lipoide im menschlichen Ovarium). v. Mikulicz-Radecki (F.), Arch. f. Gynäk. (Berl.), 1922, **116**, 203-251.

Human ovaries from the 3d fetal month to the climacteric were analyzed for their fat content. The details of the results are too extensive for concise abstracting. Marked differences in amount and distribution of the various general types of lipoids were found A good review is given.—F. S. H.

(GONADS) A case of infantilism. Miura (H.) & Numata (S.), Tokyo Iji-Shinshi, 1922, No. 2287, No. 2288 (July); cit., Jap. Med. World (Tokyo), 1922, **2**, 324.

(GONADS) Primary OVARIAN exophthalmos. Nishioka (M.), Chugwai Iji-Shimpo, 1922, No. 1016 (July); abst., Jap. Med. World (Tokyo), 1922, **2**, 326.

The author reports a case of exophthalmos, which was completely and rapidly cured by the extirpation of a diseased ovary in a woman of 25 years. He concludes that the ovarian affection caused the development of exophthalmos.—R. G. H.

(GONADS) TESTIS opotherapeutics. Pavlov (M. M.) & Popov (N. W.), Vrach. Delo, 1919, No. 17, 570-579.

Under the influence of a protein-free extract of the testis the blood pressure temporarily falls, the pulse pressure increases, and a slowing of the heart is observed. The authors suggest that testicular extracts oxidise **adrenaline** in the blood and thus moderate its action on the vascular system.—Physiol. Abst., **7**, 615.

(GONADS) Interstitial tissue and secondary sex characters in birds. Response to J. Benoit (Tissu interstitiel et caractères sexuels secondaires des oiseaux. Reponse à J. Benoit). Pézard (A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 245-247.—T. C. B.

(GONADS) Criticism of the theory of Bouin and Ancel (Critique de la théorie de Bouin et Ancel). Pézard (A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 333-335.—T. C. B.

(GONADS) Action of the PLACENTA optone (Wirkung der Placentaoptone). Puppel (E.), Arch f. Gynäk. (Berl.), 1922, **116**, 577.

Rabbits were used in these experiments. They were injected with placenta extracts and for comparison with **thyroid** and **ovarian** extracts. The placenta extract alone caused uterine enlargement which is considered as an active growth and not an edematous or inflammatory response. The result is considered as evidence for the specificity of the hormone.—F. S. H.

(GONADS) Structure of the TESTICLE of the chimpanzee and the physiological results of grafting (Structure des testicules d'un

chimpanzé et resultats physiologique de leur greffe). Retterer (E.) & Voronoff (S.), Compt. rend. Soc. de biol. (Par.), 1923, **88,** 339-340.—T. C. B.

(GONADS) Feeding experiments on tadpoles: PROSTATE gland and other substances. Rogoff (J. M.) & Rosenberg (W.), J. Pharmacol. & Exper. Therap. (Balt.), 1922, **19,** 353-358.

Tadpoles were fed human prostate and commercial preparations of ram's and bullock's prostate. Fresh liver, boiled liver, lymph glands, cattle blood serum, cracker dust and brewer's yeast were used as control feeding substances. The authors conclude that a number of substances may increase growth or hasten slightly metamorphosis, but there is no evidence that any of these substances including prostate has a specific effect comparable to that caused by thyroid feeding.—G. E. B.

(GONADS) Nervous symptoms of endocrine origin in women and treatment with ovobrol (Nervöse Erscheinungen auf innersekretorischer Basis bei der Frau und deren Behandlung mit Ovobrol). Runze, Fortschr. d. Med. (Berl.), 1922, **40,** 665-667.—J. K.

(GONADS) Unilateral gynecomastia (Eenisidig gynækomasti). Sand (K.), Festskr. til Thorkild Rovsing (Copenhagen), 1922, April 26, 8pp.

The author discusses the relations between the physiology of the mamma and the sexual glands. He reports the case of a young man of 21 years who desired amputation of the right mamma, which was often tender upon pressure and which handicapped him as a sportsman. The left mamma was normal; the right mamma presented a virginal aspect. Otherwise he appeared absolutely virile—the genital organs were normal and his sexual life was natural. The right mammary gland was subcutaneously amputated. Microscopic examination showed connective tissue with few cells, containing dispersed acini; here and there they were somewhat dilated, but in other respects the construction was like that of virginal mammal tissue. No signs of tumor were apparent.—K. H. K.

(GONADS) Hermaphroditismus (verus) glandularis alternans in a child of 10 years. Sand (K.), Ugesk. f. Læger (Copenhagen), 1922, **84,** 921-933.

The case is described of a "boy" of 10 years whose parents are uncertain concerning his sex. His aspect is predominatingly masculine, although he has weak and fine features. He presents labia majora, very small labia minora, a vulva and a very hypertrophic clitoris, 5 cm. long. The orifice of the urethra is slightly behind the clitoris. Psychically he presents both boy-like and maiden-like features; he is very intelligent. Exploratory laparotamy presented a small uterus and fallopian tube with fimbriae at each side. At

the right side there was a testis-shaped body, at the left side a somewhat larger ovary-shaped body. Small pieces of each of the glands were removed. Microscopical examination of the first showed the picture of a testis of fetal structure; the other showed a very complicated picture similar to an abnormally differentiated ovary from an early fetal stage. The case belongs to the very rare class of true glandular hermaphroditism. The author considers the difficulties in therapy and discusses its significance from the endocrine point of view.—K. H. K.

(GONADS) Action of the CORPUS LUTEUM on the genital organs (L'appareil lutéinien de l'ovaire. Son action sur les organes génitaux). Schil, Paris méd., 1923, **13,** 138-141.

A general review without bibliography.—R. G. H.

(GONADS) Psuedohermaphroditismus internus masculinus. Seedorff (M.), Hosp.-Tid. (Copenhagen), 1921, **64,** Dansk kir. Selsk. Forhandl., 90.

A man, aged 24 years, virile of aspect, was operated upon for bilateral inguinal hernia. At the right side there was a large retained **testis,** epididymus, etc. At the left side there was a normal looking large testis in the bottom of the scrotum, with vas deferens and funiculus; in addition, in this half of the scrotum was a uterus as big as a thumb, with a wide cavity and with a stalk-like structure which entered into the pelvis. Microscopically, it presented a normal uterine structure with typical glandular elements. The sexual life of the patient had never presented any abnormality. —K. H. K.

(GONADS) Quantitative variations of the glandular and non-glandular interstitial tissue of the TESTICLE of b.rds with a periodic sexual activity (Sur les variations quantitatives des tissus interstitiels glandulaire et non glandulaire dans le testicule des oiseaux à activité sexuelle périodique). Benoit (J.), Compt. rend. Soc. de biol. (Par.), 1923, **88,** 205-207.—T. C. B.

(GONADS) A case of EUNUCHOIDISM. Sumiwo (S.), Chugwai Iji-Shimpo, 1922, No. 1013; cit., Jap. Med. World (Tokyo), 1922, **2,** 325.

(GONADS) Concerning Steinach's F-cells (Zur Frage von Steinach's F-Zellen). Scheunig (F.), Arch. f. Gynäk. (Berl.), 1922, **116,** 660-683.

Discussion and histological study of human testes in embryonic and fetal stages. It is concluded that the male puberty-gland cells are of germinal epithelial origin; they are "genitaloid" cells. They reach their maximum development at the end of the fourth fetal month and decrease with the sudden increase in the germ elements

in the fifth month. Whether the interstitial cells are incretory cells is not determined.—F. S. H.

(GONADS) Malignant tumors of the TESTIS. Schultz (O. T.), Chicago Path. Soc., 1921, **11**, 185-195.

Schultz made a study of 15 malignant tumors of the testis sent to the pathological laboratory of Michael Reese Hospital. He concludes that sarcoma of the human testis is rare. The few undoubted spindle cell sarcomas which have been reported appear to have arisen in the tunics of the testis or epididymus. The vast majority of malignant tumors of the testis are epithelial. These tumors fall into two main groups. In one the atypical tissue is solid, medullary and composed of closely packed large polyhedral cells. To this type the term sarcoma is frequently misapplied. The large cell medullary tumor is derived from the germinal epithelium of the seminiferous tubules. For this the name spermatocytoma is suggested. In the second group the atypical tissue has a glandular or papillary character. Most tumors of this group contain heterologous tissues. All are probably teratomatous in origin. For this kind of tumor Ewing's designation of embryonal carcinoma may be retained. The embryonal carcinoma may be further subdivided according to the origin of the proliferating epithelial elements: hypoblastic (characteristically adenocarcinomatous; trophoblastic (chorioma); epiblastic (solid, nonglandular alveoli of basal cell type, or rosettes of neuroepithelial origin).—J. P. S.

(GONADS) The pathogenesis of meno- and metro-rrhagia (Beiträge zur Pahtogenese der Meno- und Metrorrhagien). Seitz (A.), Arch. f. Gynäk. (Berl.), 1922, **116**, 252-290.

A good review in which endocrine factors of ovarian origin are included.—F. S. H.

(GONADS) The use and abuse of CORPUS LUTEUM extract in the toxic vomiting of early pregnancy. Taylor (J. S.) & Taylor (S. P.). Penn. M. J. (Harrisburg), 1923, **26**, 252-255.

A few speculations regarding the function of the corpus luteum are offered and arguments for and against the use of this substance in the toxic vomiting of pregnancy are advanced. Of little endocrine interest.—I. B.

(GONADS) The use of small doses of x-rays in amenorrhea and other cases of hypo-ovarianism (Uber die Awendung kleiner Röntgendosen bei Amenorrhoe und anderen auf Unterfunktion der Ovarien beruhenden Anomalien). Thaler (H.), Klin. Wchnschr. (Berl.), 1922, **1**, 2454.

No details are given.—J. K.

(GONADS) Case of virginal menorrhagia (Un case rebelle de ménorragie virginale). Van der Elst (M.), Gynéc. et Obst. (Par.), 1922, **6**, 434-436.

A patient of 19 was troubled with constant uterine hemorrhage resulting in anemia, vertigo, dyspnea, constipation, vomiting, and lack of appetite. Cardiac, renal or hepatic etiology were not sustainable. The slight retroflexion of the uterus, or a possible ovarian sclerosis were not obvious causative factors. Treatment with pitréanaline followed by ovarian opotherapy gave relief.

—F. S. H.

(GONADS) TESTICULAR grafts (Injertos testiculares). Voronoff (S.), Arch. de med., cirug. y espec. (Madrid), 1922, **9**, 97-106.

Voronoff reviews his work during the past 4 years on gonad transplantation. He believes that the incretion that the transplanted testicle adds to the blood stream stimulates the activity of all organs. He claims that the infirmities of old age, both physical and mental, can be combatted by gonad transplantation. Whether we shall be able by means of the same medium to prolong life, Voronoff believes that our experiences are of too recent date to determine with respect to man, but states that the life of animals has been prolonged in this way, citing as an instance rams that have lived 3 or 4 years longer than their usual maximal age after having been subjected to this operation.—W. H.

(GONADS) The influence of the internal secretions on the development of the secondary sex characteristics (Der Einfluss der inneren Sekretion auf die Ausbildung der sekundären Geschlechtsmerkmale). Weil (A.), Arch. f. Frauenk. u. Eugenik. (Leipz.), 1922, **8**, 118-126.

A brief review of some of the important literature leads the author to the conclusion that secondary sexual differentiation can be explained by assuming differential degrees of incretory gland activity.—R. G. H.

(GONADS) Body structure and psychosexualism (Körperbau und psychosexueller Charakter). Weil (A.), Fortschr. d. Med. (Berl.), 1922, **40**, No. 22-23 (June).

Ten subjects of psychosexual infantilism showed a fairly symmetrical decrease in the standard skeletal measurements. Four homosexual males were somewhat long legged and in pelvic and shoulder measurements approached the feminine type. Ten women of the virile type tended toward masculine pelvic and shoulder measurements.—R. G. H.

(GONADS) Comparative microchemical researches on the content of the interstitial and of the lutein cells in the OVARY of the rabbit (Ricerche comparative di microchimica sul contenuto delle cellule

midollari e luteiniche dell' ovaia di coniglia). Zalla (M.), Arch. ital. di anat. e di embriol. (Firenze), 1921, **18**, 475-484.

Four rabbits were studied, two pregnant, one killed immediately after delivery and one 40 days after delivery, the findings being essentially the same in all. For numerous tinctorial reactions the original may be consulted.—G. V.

Evolution of the hormone of the infundibulum of the PITUITARY gland in terms of histamine, with experiments on the action of repeated injections of the hormone on blood pressure. Abel (J. J.) & Rouiller (C. A.), J. Pharmacol. & Exper. Therap. (Balt.), 1922, **20**, 65-84.

A method is described for obtaining from the posterior lobe of the hypophysis a pressor-oxytocic principle which is equal in oxytocic activity to from 12 to 18 times its weight of histamine hydrochloride. The first intravenous injection is followed by a pure pressor effect, while a later injection gives a distinct fall in blood pressure. The secretion of urine in the rabbit is reduced or inhibited altogether by a small intravenous injection. It is believed that the vasomotor, oxytocic and renal actions are all effected by a single hormone in the preparation.—G. E. B.

Action of HYPOPHYSEAL extract (Experimentelle Untersuchungen über die Wirkungsweise der Hypophysen extrakte). Anderes, Arch. f. Gynäk. (Berl.), 1922, **117**, 299-301; see also, Klin. Wchnschr. (Berl.), 1922, **1**, 1760.

Inconclusive results.—F. S. H.

Influence of extract of HYPOPHYSIS on the imbibition of tissues. (Influence de l'extrait d'hypophyse sur l'imbibition des tissus). Biasoti (A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 361-362.—T. C. B.

(HYPOPHYSIS) Sisters with dystrophia adiposogenitalis (Geschwisterpaar mit adiposo-genitaler Dystrophie). Biedl, Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1630.

Demonstration of two patients and a photograph of a third case. In these cases not the slightest symptoms suggesting hypophyseal disorders existed. The author believes, however, that there exists a cerebral adiposity, with an important metabolic center located in the interbrain, and that cerebral as well as hypophyseal cases of Fröhlich's syndrome probably occur. The same is true of **diabetes insipidus.**—J. K.

Common PITUITARY syndromes. Blumgarten (A. S.), Med. Clin. N. Am. (Phila.), 1922, **6**, 687-718.

In this paper are included reports of 2 cases of pituitary tumor and 4 cases of functional pituitary syndrome characterized by

abdominal manifestations. The symptoms of pituitary tumor are referable to (1) intrasellar pressure, especially headache, vomiting, and eye symptoms; and (2) disturbances of genital function, of bony growth, of carbohydrate metabolism, and of salt and water metabolism. Functional pituitary syndromes are due to physiological or pathological hypertrophy of the pituitary, giving rise to intrasellar pressure plus abdominal cramps which may resemble the symptomatology of such abdominal lesions as gastric ulcer, gall bladder disease, appendicitis, ureteral affections, and the like. Attacks of colic are always preceded by characteristic supra-orbital and bitemporal headache, which is frequently assocated with blurring of vision and dizziness. Treatment of the syndrome consists in the administration of pituitary extract, supplemented if necessary by antispasmodics, **corpus luteum**, and a protein-free diet.—I. B.

Uterus rupture after one injection of HYPOPHYSIS extract (Rupture de l'utérus après une injection d'extrait hypophysaire). Sejournet & Braine, Gynéc. (Par.), 1922, **24**, 618.

The effect of HYPOPHYSEAL extracts upon the water metabolism of the frog (Beitrag zur Kenntnis der Wirkung von Hypophysenextrakten auf den Wasserhaushalt des Frosches). Brunn (F.), Ztschr. f. d. ges. exper. Med. (Berl.), 1921, **25**, 170-175.

Pituitrin does not affect the intact frog's urine secretion, although perfusion of the isolated frog kidney with a pituitrin solution causes contraction of the glomerular vessels. Pituitrin has a specific effect only upon extrarenal water metabolism. Frogs kept in water without nourishment do not appreciably vary in weight. After subcutaneous or intravenous injection of 1 cc. pituitary extract (various preparations were used) weight increased on an average of 12%, with the maximum after 8 to 12 hours and a return to normal usually in 24 to 36 hours, but in some cases 3 to 4 days. Extirpation of frog kidneys showed that the weight increase did not depend upon hindrance of urine secretion. The weight of nephrectomized frogs increased at first about 2 gm. daily, and gradually increased. The frogs usually died on the fifth day from extensive edema. Injection of pituitrin on the day following the operation caused sudden increase of body weight. Exsiccation of frogs in wire cages was not retarded by pituitrin, nor did exsiccated frogs if brought into water reach normal weight more quickly. The pituitrin-water-retention in the frog differs from that of man only in extrarenal factors.—A. B.

Reports on biological standards. I. PITUITARY extracts. Burn (J. H.) & Dale (H. H.), Med. Res. Coun., Spec. Rep. Ser., 1922, No. 69.

Using the isolated uterus of the virgin guinea pig as a test for making quantitative estimations of pituitary extracts, it is found

that the only suitable standard for comparison is a preparation of the pituitary extract itself. Chemical substances such as histamine or KC1 are of no use, because the sensitiveness of different uteri varies differently towards a pituitary extract on the one hand from the variation to histamine or KC1. It is shown that, unlike the **suprarenal** gland, in which the amount of active principle varies in different animals, the pituitary glands of oxen contain approximately the same amount of activity per gm. of material, even though the glands are obtained at different seasons of the year. Consequently, provided the process of obtaining and extracting the glands is kept constant in all details, an extract of fresh glands may serve as a standard of reference for commercial extracts made by large scale methods. A considerable part of the variation observed in commercial extracts at present on the market is due to the fact that different manufacturers make extracts of different strengths. It is recommended that all extracts should be 10%.—Physiol. Abstr., **7**, 612.

Tumors of the HYPOPHYSIS. Cohoe (B. A.), Penn. M. J. (Harrisburg), 1923, **26**, 328-330.

A brief description of the symptomatology of pituitary tumor, and the report of a case. The patient was a married woman of 59 in whom an adenoma of the pituitary progressed to the stage of rupture on the floor of the sella and invasion of the sphenoidal cells. The local pressure effects of the mass on neighborhood structures were so striking as to render inconspicuous the signs of any functional involvement of the gland. Operation was performed by Dr. Cushing. One month later, following a brief improvement in vision, the sight again began to fail. A course of radium treatment yielded no improvement. The administration of pituitary extract was likewise a failure. Subsequently, however, though the vision was about the same, the general condition of the patient was good, and there were no evidences of pituitary hypofunction.—I. B.

Concerning some of the ocular interpretations of disorders of the PITUITARY body and their non-surgical treatment. deSchweinitz (G. E.), Virginia M. Month. (Richmond), 1921, **48**, 179-183.

A discussion of the ocular manifestations commonly present in pituitary body disorders, and suggestions in medicinal treatment. Impairment of vision may vary from a mere blurring of sight to complete blindness, according to the degree of disturbed function of the optic pathways. This, in turn, depends upon the degree of compression of the chiasm, tracts, and optic nerves, but does not bear any close relation to the size of the sella. For instance, in **acromegaly**, the size of the sella may be conspicuous, but the vision is good. Other eye phenomena associated with pituitary disorders are lesions of the optic nerve, alterations of the visual field, and anomalies of ocular motility. In general, deSchweinitz has had

excellent results in the treatment of these patients by large doses of extract and average doses of the iodides and mercurial inunctions. An occasional instance may present indications for pituitary opotherapy as well. Though the patient's luetic history and Wassermann reaction may be negative, syphilis may be present. These patients usually show a marked tolerance to mercury, and its exhibition is always advantageous. There is a probable synergistic relationship between thyroid extract, pituitary substance, and mercury. Radium is also of value in the treatment of hypophyseal lesions.
—I. B.

(HYPOPHYSIS) Menstrual hemoptysis. Its preventive treatment (Hemoptisis menstrueles. Su tratamiento preventivo). Destefano (J.), Semana méd. (Buenos Aires), 1923, **30**, 52-53.

Menstrual hemoptysis of tuberculosis can be prevented by intravenous injection 10 days before menstruation of 0.5 to 1 cc. of hypophysis extract, diluted in 10 cc. of saline water. This injection should be repeated every 48 hours up to the appearance of menstruation.—B. A. H.

The influence of the HYPOPHYSIS on the dysfunction of the genital organs (Ueber den Einfluss der Hypophyse auf die Dysfunktion der Genital organe). Dietrich, Arch. f. Gynäk. (Berl.), 1922, **117**, 298-299.

See Endocrin., **2**, 172.

(HYPOPHYSIS) Acromegaloidism (Uber Akromegaloidismus). Ehrmann (R.) & Dinkin (L.), Klin. Wchnschr. (Berl.), 1922, **1**, 2139.

The authors believe that sometimes patients with seeming complaints of rheumatic origin suffer instead from a constant, nonprogressing hypersecretion of the anterior lobe of the normal hypophysis. They believe this to be a typical clinical picture, which they call "acromegaloidism" or "acromegaloidismus rheumatoides." During 5 years they examined over 40 cases; radiographic examinations of the skulls showed that 14 patients had large sellas. The lower jaw, lips, tongue, hands and feet were more or less of the acromegalic type. Very often these cases are familial.—J. K.

HYPOPITUITARISM (the hypophysopathies). Engelbach (W.) & Tierney (J. L.), Med. & Surg. (St. Louis), 1918, **2**, 193-202.

A detailed report of the case of a woman aged 35 years. The short long bones, short stature, virgin mammae, absence of hair under the arms, and absence of girdle obesity with many years of continuous complete amenorrhea led to the diagnosis of preadolescent hypopituitarism.—J. P. S.

Diseases of the pituitary gland (HYPOPHYSIS cerebri). Engelbach (W.) & Tierney (J. L.), Med. & Surg. (St. Louis), 1918, **2**, 466-486.

A detailed report of the case of a school boy 14 years of age. Diagnosis was as follows: Hypopituitarism, posterior lobe insufficiency without anterior lobe involvement; preadolescent variety; neoplastic type. This diagnosis was made on the basis of (1) objective evidence, such as enlargement of the sella turcica, blindness, and symptoms of intracranial pressure; (2) history of early diabetes insipidus followed in a short time by disturbances of vision and ultimately total blindness; and (3) overdevelopment of the long bones and well developed genital organs which indicate sufficiency of the anterior lobe.—J. P. S.

HYPOPITUITARISM (hypophysopathies). Posterior lobe insufficiency. Engelbach (W.) & Tierney (J. L.), Med. & Surg. (St Louis), 1918, **2**, 549-577.

A detailed report of the case of a man aged 35 years with a diagnosis of hypopituitarism, posterior lobe insufficiency occurring after adolescence, and associated with a neoplasm of the pituitary gland. This diagnosis was based on the presence of polyphagia, polydipsia and polyuria, with extreme emaciation, marked nervousness and bilateral homonymous hemianopsia. An operation resulted in some improvement of the condition and the patient was still alive a little more than a year after the operation.—J. P. S.

PITUITARY obesity. Engelbach (W.) & Tierney (J. L.), Med. & Surg. (St. Louis), 1918, **2**, 737-766.

A detailed report of a case of hypopituitarism, bilobar in distribution, of the preadolescent variety, without neoplasm.—J. P. S.

Experimental lesions of the HYPOPHYSEAL region and polyuria. Hanchett (McM.), Proc. Inst. Med. Chicago, 1921, **3**, 202-207.

Hanchett made the following studies on dogs: (1) stimulation of the anterior part of the hypophysis: (a) varying degrees of heat applied with a heated rod or with paraffin; (b) trauma pinching and pulling with tissue forceps; (c) cone-shaped plug of beeswax pushed into the opening in the bone; (d) induced current—electrical; (2) herniation of the gland through the dural opening; (3) traction on the base of the brain with as little trauma to the gland as possible; (4) effect of pituitary extract, **epinephrin** and **thyroid** extract on polyuria. While admitting that it is impossible to regulate accurately the degree and extent of the injury inflicted to the gland and its neighboring structures, Hanchett states that he found no urinary increase of any consequence in any of the animals in which either the anterior or posterior lobes individually or the entire gland itself were stimulated by nondiffusable means, i. e., heat or mechanical trauma. Stimulation of the hypophysis

with an induced current produced polyuria. However, as an electric current may be transmitted over a considerable distance, it cannot be said that this trauma was limited to the gland itself, or that the urinary increase was of hypophyseal origin. By traction on the stalk with effort to avoid trauma to the gland itself, Hanchett states that he was able to produce polyuria regularly. He was able also to regulate the degree of this increase, moderate or extreme, by modifying the amount of traction exerted. Other animals operated upon, in which the same procedure was followed except for traction on the stalk, showed no or only slight polyuria. The 3 outstanding experiments to which the author calls special attention were those on dogs 2, 15 and 55. In dog 2, the opening in the sphenoid bone was made so far posterior that the hypophysis was not exposed, and the stimulation (cauterization) was applied to the region of the corpora mamillaria. In dog 15, due to peculiar anatomic arrangements, the gland came through the dural incision with considerable force, followed by a larger amount of cerebrospinal fluid than had usually been observed. Except for these variations nothing was done which had on previous occasions produced more than a negligible increase in urinary secretion. In dog 55 there was found at postmortem examination a hemorrhage into the third ventricle. The associated polyuria was most marked in this group. Hanchett concludes that "polyuria associated with pituitary disease is, to borrow an expressive phrase, a 'neighborhood symptom'."—J. P. S.

Normal diuresis and diuresis due to HYPOPHYSECTOMY (La diuresis normal y provocado de los perros sin hipofisis). Houssay (B. A.) & Hug (E.), Rev. Asoc. med. argent. (Buenos Aires), 1921, **34**, Sec. Biol., 56-61.

Hypophysectomized dogs usually have urinary output normal in quantity and quality, though in the first few days transitory polyuria is sometimes seen. Water administered by mouth is eliminated more slowly in these dogs,—46% in 3 hours instead of 60%, the rate in the controls.—B. A. H.

Polyuria by extirpation of the HYPOPHYSIS in dogs with denervated kidneys (Polyurie par extirpation de l'hypophyse chez des chiens à reins énervés. Houssay (B. A.) & Rubio (H.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 358-359.—T. C. B.

Disease of the HYPOPHYSIS (Hypophysenerkrankung). Jungmann, Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1628.

The disease began with symptoms of **diabetes insipidus** (thirst, polyuria). Later, these symptoms became much less intense and only an increased NaCl production and general hyperosmosis of the blood remained. At postmortem examination, purulent appendicitis and an abscess of the hypophysis were detected. The author explains the improvement of the diabetes insipidus by stating that

pressure of the abscess on the interbrain was lessened as the symptoms of the inflammation became less intense.—J. K.

Blindness of PITUITARY origin and organotherapy. Kern (M.), Am. J. Clin. M. (Chicago), 1923, **30**, 18-22 (January).

Detailed case report with theoretical discussion. The "organotherapy" (nature not specified) resulted in spectacular restoration of vision.—R. G. H.

(HYPOPHYSIS) The practical importance of some obstetrical methods (Over die practische waarde von eenige obstetrische handelingen). Koek (C.), Inaug. Dissertation, Leiden, 1922.

Dutch opinion differs as to the value of pituitrin. Kouwer, professor of obstetrics at the University of Utrecht, opposes its use (see Endocrin., 1922, **6**, 156, 314). Koek sent questionnaires to all Dutch doctors who practice obstetrics. Eighty per cent of these doctors used pituitrin; 7% were not satisfied. Most of these complained of the inactivity of the drug. This is probably because the Dutch preparation (pituitrin-Blomberg) is often inactive. Some complained that pituitrin would sometimes cause spasms of the ostium uterinae, and difficulty in removing the placenta. Some thought that pituitrin endangered the life of the child, and that it would sometimes produce collapse in the mother, especially during the first hour after birth. Most of the physicians reported that pituitrin lessens the time of labor and decreases the use of forceps.—J. K.

(HYPOPHYSIS) Diagnosis of the lesser hypophyseal syndromes (Diagnostic des petits syndromes hypophysaires). Léopold-Lévi (M.), Médicine (Par.), 1923, **4**, 342-348.

Léopold Lévi divides the syndromes of the hypophysis into hypopituitarism, hyperpituitarism, and instability of the hypophysis. He analyzes their morphologic, nervous, visceral, and metabolic symptoms in the different stages of the evolution, expressing his ideas in detailed tables of symptoms.—R. G. H.

PITUITRIN in obstetrics. Mendenhall (A. M.), Indianapolis M. J., 1921, **24**, 191-196.

Mendenhall calls attention to the many dangers in using pituitrin in obstetrics and advises its use only in selected and carefully supervised cases.—F. C. P.

(HYPOPHYSIS) A case of acromegaly. Okabe (Y.), Fukuoka Ikadaigaku Zasshi, 1922, **15**, No. 4 (July); cit., Jap. Med. World (Tokyo), 1922, **2**, 329.

HYPOPHYSIS and pregnancy (Hipófisis y gestacion). Perez (M. L.), Semana méd. (Buenos Aires), 1921, **28**, 540-548; 580.

General description of the anatomy, embryology, histology and physiology of the hypophysis. The author observed 10 pregnant, 9 nonpregnant and 4 male, hypophysectomized dogs. All of the pregnant females died within 24 hours. Mortality in the other animals was about 60%.—B. A. H.

The basal metabolism in HYPOPHYSEAL diseases (Ueber den respiratorischen Gasswechsel bei Erkrankungen der Hypophysis). Plaut (R.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1413.

See Endocrin., **6**, 715.—J. K.

A case of meningeal endothelioma simulating a tumor of the HYPOPHYSIS. Portis (B.), Tr. Chicago Path. Soc., 1922, **11**, 303-306.

Report of a case of a woman aged 50 with autopsy findings of an endothelioma of the meninges extending over the hypophysis with pressure enlargement of the sella turcica. The woman was very obese.—J. P. S.

Some lesions of the HYPOPHYSIS. Simonds (J. P.), Tr. Chicago Path. Soc., 1921, **11**, 183-185.

A small abscess in the posterior hypophyseal lobe was reported from a patient with multiple septic infarcts, also a condition in which the cells from the middle lobe grow backward into the neurohypophysis. This condition is relatively common in old age. Islands of abnormal cells in the posterior lobe were also described. These cells are unlike any of the cells of the anterior or middle lobes, and are not connected, as shown by serial sections, with the backward growth of cells from the middle lobe. Their significance is unknown. Hemangioma-like structures were found in the anterior lobe. These appear to be quite constant and can be readily demonstrated by serial sections. Small masses of lymphoid cells were occasionally found along the line of junction between the middle and posterior lobes. Their significance is not known. Congenital syphilis of the hypophysis, the characteristic feature, is a rather uniform increase of connective tissue between the cords of cells in the anterior lobe. An adenoma of the hypophysis was also reported from a patient with no acromegaly or other disorder of the hypophysis.—Author's Abst.

Action of extracts of HYPOPHYSIS on bulbar polyuria (Action des extraits d'hypophysis sur la polyuria bulbaire). Solari (L. A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 359-360.

Case of dwarf having PITUITARY derangement. Takimoto (S.), Chugwai Iji-Shimpo, 1922, No. 1013, 1014; cit., Jap. Med. World (Tokyo), 1922, **2**, 325.

The influence of PARATHYROID and THYROID tissue on the creatinine-creatine balance in incubated extracts of muscle of the albino rat. Hammett (F. S.), J. Biol. Chem. (Balt.), 1921, **48**, 143-152.

Evidence is presented which demonstrates that the addition of parathyroid tissue to extracts of muscle tissue tends to retard the formation of creatinine normally taking place during incubation. This occurs in acid neutral or alkaline mixtures. The addition of thyroid tissue to similar extracts has no effect upon the creatinine formation that is demonstrable by the methods used. Since the maximum retardation effect of the parathyroids occurs in solutions buffered to neutrality, while the maximum creatinine formation takes place at the same reaction, the conclusion is justified that this parathyroid effect is an expression of a direct influence of the parathyroids on creatine metabolism.—F. S. H.

(PARATHYROID) The influence of TETANIA gravidarum on the young (Ueber den Einfluss der Tetania gravidarum auf die Frucht). Niderehe (W.), Arch. f. Gynäk. (Berl.), 1922, **116**, 360-382.

The possibility of a parathyroid insufficiency being a contributing factor is briefly mentioned.—F. S. H.

Studies in the physiology of the PARATHYROIDS. Salvensen (H. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, 204-210.

After partial **thyroidectomy** in dogs there was a 30% reduction in the serum calcium. After complete parathyroidectomy in 10 dogs, 6 died of tetany. These showed decreased calcium and increased phosphorus in the serum. After intravenous injections of calcium chloride the calcium injected was excreted within 24 hours, largely into the bowel. Four of the parathyroidectomized animals were kept healthy on a diet containing a liberal supply of milk. The calcium in the milk was the essential factor. The calcium of the blood remained low. There was a relation between the tolerance for glucose and the amount of blood calcium. In convulsions produced in healthy animals by guanidin there is no reduction of serum calcium.—J. C. D.

PARATHYROID therapy in calcium deficiency. Vines (H. W. C.), Dementia Praecox Studies (Chicago), 1922, **5**, 69-75 (April).

In chronic ulcerative states in which there is chronic toxemia the author has found uniformly a reduction in the ionic calcium of the serum. This is dependent upon partial parathyroid deficiency. In treating these cases, calcium salts alone give no improvement, but when given with parathyroid, 1/10 grain every other day, marked improvement has resulted. More than 100 cases have been

dealt with. Vines believes that clinical evidence supports MacCallum's theory that toxic substances may arise under conditions of parathyroid insufficiency and form combinations with calcium of blood. A short bibliography is appended.—F. H. A.

Physiology of the PINEAL body. Izawa (Y.), Okayama Igakkwai Zasshi, 1922, No. 390 (July).

The endocrine organs that are affected by pinealecotomy are genital glands, i. e., the **testes**, the **ovary** and fallopian tubes, besides combs and the bodily development.—Jap. Med. World, **2**, 333.

On the influence of the SPLEEN upon red blood-corpuscles. Bolt (N. A.) & Heeres (P. A.), Biochem. J. (Lond.), 1922, **16**, 754-764.

Material from sheep was used. The spleen has the power of diminishing the osmotic resistance of the erythrocytes. These are prepared hereby for hemolysis which partially takes place in the organ itself. Erythrocytes from the vena lienalis that have been washed with an equilibrated salt solution do not show this decreased osmotic resistance. This fact is taken to prove that the point of attack of the hemolytic power of the spleen lies in the removable surface layer of the erythrocytes. The alteration in this layer must consist in a decrease of the proportion cholesterol phosphatide. —F. S. H.

A new function of the SPLEEN (Ueber eine neue Funktion der Milz). Naswitis (K.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1441.

Blood, hemolyzed by freezing and heating, was intravenously injected into dogs from which the blood had been taken. There resulted an increase of the quantity of blood. This was not true, however, when the same experiment was performed on splenectomized dogs. The author concludes that hemolyzed blood does not stimulate directly the blood preparing organs, but that it stimulates the formation in the spleen of substances acting upon the bone marrow. He believes, therefore, that the spleen is probably the "higher center" of the bone marrow, regulating its activity by hormones.—J. K.

Two cases of sclerema neonatorum and hypertrophy of the THYMUS (Due casi di sclerema dei neonati con ipertrofia del timo). Buscemi-Grimaldi (A.), Arch. di farmacol. sper. (Roma), 1922, **34**, 94-107; 113-117.

A hyperplastic condition of the thymus associated with complete absence of eosinophil cells in the same organ were the only histopathological lesions found in 2 cases of sclerma neonatorum. —Physiol. Abst., **7**, 619.

(THYMUS) A study of the shadows in the thorax of the newly-born. De Buys (L. R.) & Samuel (E. C.), Am. J. Dis. Child. (Chicago), 1922, **24**, 397-404.

This study, based upon the observations in 55 infants, was undertaken with the hope of devising some method by which the abnormal shadows in the thorax of the newly-born could be differentiated from the normal. The conclusions obtained were as follows. The heart shadows vary as to shape, size and position. These variations occur with no relation to the size of the infant. The heart shadows may be grouped in several types according to shape, such as globular, adult, drop, nutmeg, round, unusual and unclassified. Variations in size and position occur in each of these types. There is no constant relation between the heart shadow and the shadow of the thymus. The shadow of the thymus is not necessarily influenced by the position of the heart. The shadow of the thymus varies in its size and position independent of the heart shadow and with no relation to the size of the infant. These variations in the shadows of the heart and thymus can exist without clinical manifestations of disease.—M. B. G.

The incidence of THYMIC enlargement without symptoms in infants and children. Greenthal (R. M.), Am. J. Dis. Child (Chicago), 1922, **24**, 433-441.

An analysis of 2,000 consecutive cases in infants and children ranging in age from 3 days to 12 years. Thymic enlargement was diagnosed in 90 or 4.5%. Of these 90 patients, 87 gave no history and presented no symptoms of thymic involvement. Enlargement of the thymus was noted in 25.6% of all the patients who had a roentgenogram of the thorax made. The finding of an enlarged thymus gland even though there be no clinical evidences of thymic involvement should not be treated lightly. Greenthal believes that pre-operative x-ray treatment of patients who have enlarged thymus lowers the number of operative deaths. Congenital defects and malformations are frequently found associated with enlargement of the thymus. An enlarged thymus has been frequently found in poorly nourished and marantic children. On the other hand, Greenthal noted that just as frequently has he found no thymic enlargement in well nourished children.—M. B. G.

Two cases of sclerema neonatorum with hypertrophy of the THYMUS (Duo casi di sclerema dei neonati con ipertrofia del timo). Grimaldi (A. B.), Arch. di Farmacol. sper. (Roma), 1922, **34**, 95-107; 113-117.

A postmorten report of two female infants who died immediately after birth. Both presented evident signs of sclerema. In both, the heart, thyroid, surrenals, kidneys and liver appeared normal, while their thymus showed accentuated hypertrophy. The

chief abnormality in the thymus was the complete absence of eosinophil cells.—G. V.

THYMIC asthma. Thursfield (H.), Arch. Pediat. (N. Y.), 1923, **40**, 136-142.

All evidence, clinical, pathological and radiological, points to the excessive rarity of thymic asthma. Diagnosis of the condition is by no means easy; the most convincing syndrome is the co-existence of dyspnea with a protrusion of the manubrium sterni, abnormal dullness to percussion in this region and a palpable and visible tumor during inspiration in the episternal notch. Thymectomy is rarely indicated; x-ray therapy is preferable. In the rare cases where the diagnosis is reasonably certain and relief is urgently required, thymectomy is followed by fairly good results.—M. B. G.

(THYROID) The mechanism of the so-called Abderhalden reaction (Fortgesetete Studien über das Wesen der sogenannten Abderhaldenschen Reaktion). Abderhalden (E.) & Wertheimer (E.), Fermentforsch. (Leipz.), 1922, **6**, 263-268.

The authors injected material made from thyroid into rabbits and found, some days later, thyroid-splitting enzymes. When, however, these substances were injected after thyroidectomy, no thyroid-splitting enzyme could be found. Thyroidectomy did not prevent the formation of enzymes to decompose other organs when these organs were injected. The authors consider that these experiments prove that enzymes that decompose an organ are formed in the cells of the organ itself.—J. K.

(THYROID) Some important points in the surgical treatment of toxic goiter. Alexander (J.), Penn. M. J. (Harrisburg), 1923, **26**, 256-258.

A plea for a more careful evaluation of the condition of the patient immediately prior to operation, and a description of the probable postoperative reaction to be expected. In doubtful patients and those who are seriously ill, multiple stage procedures are far safer than immediate thyroidectomy. Three case histories are appended.—I. B.

Erythropoiesis in the embryonic THYROID (Erythropoïese dans le corps thyroïde embryonnaire). Aron (M.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 193-195.—T. C. B.

THYROID and PARATHYROIDS in animals living in light or in darkness (Schilddrüse und Epithelkörpeschen bei Licht und Dunkeltiere). Ashcoff, Klin. Wchnschr. (Berl.), 1922, **1**, 1482.

A short note without details. It is merely stated that light has a more important influence on these organs than nutrition.—J. K.

Subcapsular THYROIDECTOMY in exophthalmic goiter. Asteriades (T.), Bull. méd. (Par.), 1923, **37**, 45-46; abst., J. Am. M. Ass. (Chicago), 1923, **80**, 805.

HYPOTHYROIDISM: Report of cases. Bate (R. A.), Am. Med. (Burlington, Vt.), 1918, n. s. **13**, 725-727.

This article consists of very brief reports of 10 cases, diagnosed hypothyroidism, which showed improvement under the administration of thyroid extract with "pluriglandular substances."—J. P. S.

(THYROID) Three cases of myxedema (Drei Fälle von Myxödem). Bauer (J.), Wien. klin. Wchnschr., 1922, **35**, 947-948.

Report of a woman of 48 who stopped menstruating when 37 years of age. At the age of 46 she complained of rheumatic pains in the hands, arms, legs and back. When thyroidin was given the symptoms disappeared, but as soon as the treatment was stopped the pains returned. The case is reported of a woman of 32 years whose hands and feet had been swollen a year previous to examination. Menstruation was irregular and basal metabolism was 20% below normal. The third case reported was that of a woman of 23 years, 45 kg. in weight and 136 cm. in height. One year previously a tumor in the thyroglossal duct had been removed. Histological examination showed that there was thyroid tissue in the tumor. After the operation myxedema developed with low basal metabolism and anemia. Iodine therapy had little influence, but the success obtained by thyroidin was complete.—J. K.

A case of hyperglycemia in a THYROIDECTOMIZED sheep. Bodansky (A.), Simpson (S.) & Goldberg (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 195-196.

This animal behaved atypically both in the sugar content of its blood and the response it gave to thyroxin. On autopsy, in addition to changes in the vascular system, kidneys, etc, the adrenal glands were doubled in weight and were hyperemic and hemorrhagic. The increase in size was largely in the cortex.—J. C. D.

Some new evidence regarding the control of the THYROID gland. Cannon (W. B.), Tr. N. Hampshire M. Soc. (Manchester), 1921, **130**, 144-151.

Data reported elsewhere.—W. B. C.

Nervous control of the THYROID gland. Cannon (W. B.), Northwest Med. (Seattle), 1922, **21**, 289-295.

A summary of the author's important physiological experiments demonstrating that the ductless glands are to a great extent under the control of the sympathetic nervous system. Cannon has proved this to be undoubtedly true with regard to the adrenal me-

dulla and thyroid and probably with regard to the liver. The introduction of an extremely slight amount of adrenalin into the blood stream will cause marked acceleration of the denervated heart. The same result is obtained if the afferent nerve to the adrenal gland is stimulated. Simple massage of the thyroid gland produces acceleration of the denervated heart, even when the adrenal gland has been previously removed. Likewise stimulation of the cervical sympathetic nerve will produce the same effect by increasing the output of thyroxin into the blood stream. Cannon points out a curious and interesting fact, that these experiments on the thyroid gland produced striking results (as proved by metabolism tests and electrocardiogram records) when performed on animals in November and December, whereas only minor effects and at times none at all resulted when the same experiments were repeated in March and April. The author explains this discrepancy as probably due to the marked variation of the iodin content of the thyroid gland in various seasons of the year, the high period being in September and October and the low period being in March and April. He points out that these seasonal variations in the activity of the glands of internal secretion are full of possibilities of great clinical interest. For example, in animals there are definite breeding seasons and these breeding season are definitely associated with certain periods of the year. Recent studies carried on in school children have shown that the rate of growth of school children in the fall is four times that which it is in the spring months. This suggests that there is a correlation between the rate of growth and the seasonal iodin content of the thyroid.—H. L.

Some applications of THYROID therapy. Cobb (I. G.), Prescriber (Edin.), 1922, **16**, 328-333.

In addition to its value in hypothyroidism, thyroid therapy is serviceable in chronic toxemias such as intestinal stasis, in rheumatism, and in such acute infections as typhoid fever. The author advocates the use of thyroid substance in disorders of the **pituitary, adrenals** and **thymus,** also in nocturnal enuresis and iridocyclitis. Cobb insists that in all cases the initial dose of thyroid must be small.—F. C. P.

(THYROID) Circumscribed scleroderma and exophthalmic goiter (Sclérodermie circonscrite et goitre exophtalmique). v. Dubreuilh, Bull. Soc. franç. de dermat. et syph. (Par.), 1921, **28**, 221; abst., Schweiz. med. Wchnschr. (Basel), 1922, **52**, 595.

A 53 year old woman suffered for 5 years with Graves' disease. Two years ago she developed on the upper thigh 2 symmetrical oval livid plaques.—R. G. H.

(THYROID) Some comments on the probable cause of exophthalmic goiter. Dunn (J.), Arch. Ophth. (N. Y.), 1918, **47**, 248-255.

On the basis of the work of Rosenow and Billings on focal infections and a study of 4 cases of exophthalmic goiter showing eye symptoms, Dunn concludes that the main agent at work in causing hyperthyroidism is an infectious one, and that the most common location of the focus of infection is the tonsillar crypts. The author does not offer any explanation of the mechanism by which this operates.—J. P. S.

The THYROID factor in diabète gras. Friedman (G. A.) & Gottesman (J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20**, 213-214.

A brief discussion without new facts.—J. C. D.

(THYROID) Goiter operations. Grigg (W. F.), Virginia M. Month. (Richmond), 1921, **48**, 158-160.

Advocates the use of local anesthesia in goiter operations. —J. P. S.

(THYROID: PARATHYROIDS) Concerning the formation of creatine from methyl guanidine in muscle. Hammett (F. S.), J. Biol. Chem. (Balt), 1923, **55**, 323.

Extracts of muscle tissue of the rat were incubated with methyl guanidine and the material analyzed for total creatinine. Extracts buffered with phosphate mixtures to acid and alkaline reaction, with and without the addition of sodium acetate, parathyroid tissue and thyroid tissue, were studied. Negative results were obtained throughout. No changes in the total creatinine content were observed. In view of this fact the author is inclined towards Biedl's hypothesis that methyl guanidine (supposedly found in the muscle and urine of parathyroidectomized animals) and creatine (found in the muscle tissue of normal animals) are derived from a common precursor as yet unidentified.—Author's Abst.

The refractive index and water content of the blood serum of THYROPARATHYROIDECTOMIZED and PARATHYROIDECTOMIZED albino rats. Hammet (F. S.), J. Biol. Chem. (Balt.), 1923, **55**, x.

Thyroparathyroidectomy induced an absolute increase in the refractive index and solids of the serum. No changes in the nature or the distribution of the refractive substances other than water were found in male rats. Female rats reacted differently because of more intensive growth inhibitions. Parathyroidectomy did not change the absolute amount of water in the serum or the refractive index. Nevertheless, mathematical analysis shows that the nature or the distribution of the refractive substances was altered. —Author's Abst.

THYROID therapy in eye disease. Harry (P. A.), Prescriber (Edinb.), 1922, **16**, 333-334.

Harry advocates thyroid therapy in certain forms of cyclitis, retinal and choroidal hemorrhage, vitreous opacities, optic atrophy, lesions of the cornea, parenchymatous keratitis keratoconus, corneal dystrophies, and glaucoma (when used with various myotics). He reports that myopes do not react favorably to thyroid therapy, and that thyroid amblyopia and exophthalmos may result from the injudicious use of thyroid substance.—F. C. P.

(THYROID) Hypoglycemia in exophthalmic goiter. Holman (E. F.), Johns Hopkins Hosp. Bull. (Balt.), 1923, **34**, 69-70.

Twenty-four hours after a double subtotal thyroidectomy in an exophthalmic goiter patient of 17, a condition of semi-stupor appeared. Blood sugar was found to be reduced to 48 mg. per 100 cc. Intravenous glucose relieved the condition. Further studies along this line are recommended by the author as promising valuable data.—R. G. H.

(THYROID) Endemic goiter, cretinism and their prevention (Uber endemische Struma, Kretinismus und ihre Prophylaxe). Hotz (G.), Klin. Wchnschr. (Berl.), 1922, **1**, 2073-2077.

A general review. The author believes that large doses of iodine are a better preventative against goitre than small doses.
—J. K.

(THYROID) Basal metabolism and blood sugar tolerance. Hoxie (G. H.), J. Lab. & Clin. M. (St. Louis), 1922, **8**, 112-121.

Report of a study of the relation between the basal metabolism of thyroid activity and carbohydrate tolerance. Deductions are based upon 106 tests on 95 patients. The basal metabolic rate was tested on the closed circuit type of apparatus, namely, the Sanborn Benedict and the Sanborn Handy. The amount of glucose used was 1.75 grams per kilogram of body weight according to the suggestions of Janney. The author derived the following conclusions: the simple closed circuit type of calorimeter is worth while in actual practice; variations in reports on the basal metabolism rate seem due more to the condition of the patient than to the type of apparatus; it is necessary to correlate clinical observation with the laboratory tests; the blood sugar tolerance test cannot be substituted for the calorimeter, nor can any close parallelism be drawn; both studies are needed if a complete knowledge of the patient's function and vitality is sought; a revision of terminology and standards of blood sugar curves is needed if we are to introduce this study into general practice.—I. B.

THYROID and anaphylaxis (Thyroïde et anaphylaxie). Houssay (B. A.) & Sordelli (A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 354-356.—T. C. B.

The influence of the THYROID in some acute infections. Jones (H. S.), Prescriber (Edin.), 1922, **16**, 317-322.

Since the main function of the thyroid gland is to stimulate metabolism, the activity of the gland is increased in acute infections. The author calls attention to the evidence of hyperthyroidism in acute tuberculosis of the lungs, acute articular rheumatism, diabetes, syphilis, and gonorrhea. He states that the well known effect of pregnancy on acute tuberculosis can best be explained by assuming that prior to pregnancy in a subject suffering with acute phthisis there is a pathological excess of thyroid secretion, that this excess secretion is utilized for physiological purposes during gestation and again becomes pathological after parturition and is manifested by an increased activity of the tubercular lesion. In acute rheumatism the myocardial lesions resemble those of hyperthyroidism. Diabetes is considered as an over activity of the thyroid, adrenal and pituitary associated with hypoactivity of the pancreas. Jones believes that the activity of the thyroid gland is increased in acute syphilis and gonorrhea, basing his conclusions on an army experience in which he noted that the more active the glands, the more virulent the syphilis or gonorrhea. He further calls attention to the increase of leucocytes in hyperthyroidism and points out the effect on disease.—F. C. P.

(THYROID) A study of goiter and associated conditions in domestic animals. Kalkus (J. W.), Bull. State College of Wash. Agricultural Exper. Station (Pullman), 1920, No. 156, Repr. 48 pp.

From extensive survey work and from experimentation the author reports that hyperplastic goiter is enzoötic among all species of domestic animals in certain so-called goitrous regions. It is especially prevalent in certain sections of Washington, Montana and British Columbia. The disease is manifested in somewhat different forms in the different species of domestic animals, but the primary lesion in all cases is of similar character and consists of hyperplasia of the thyroid. This type of goiter is of little importance in the adult, but causes grave disturbances in the newborn. Affected colts, kids, lambs and pigs seldom live, while the condition is less fatal to affected calves. It has not been definitely proved, but it is quite likely that a deficiency of iodine in the water, feed and possibly the soil is responsible for the malady. Other unknown factors may also be considered as causal agents. Feeding experiments indicate that either water, feed or both from a goitrous region may cause goiter. Perfectly controlled experiments with Angora goats show that goiter can be absolutely prevented by administering iodine to does during pregnancy. This can be given either in the form of potassium iodide by mouth or tincture of iodine subcutaneously or on the unbroken skin. Field experiments also indicate that the condition can be successfully prevented in

other species of animals by the use of iodine. A feature of the report is the inclusion of 29 excellent illustrations.—R. G. H.

The THYROID gland and anaphylaxis. Response to R. Applemaus (Glande thyroïde et anaphylaxie. Rèponse à R. Applemaus). Kepinow (L.) & Lanzenberg (A.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 165-166.—T. C. B.

(THYROID) Myxedema tarda in constitutional lipomatosis (Spätmyxoedem bei Konstitutioneller Lipomatose). Kisch (F.), Deutsche med. Wchnschr. (Berl.), 1922, **48**, 1644-1646.

Report of the case of a woman of 45 years, 156 cm. in height and about 95 kg. in weight. She had a broad, swollen face; big hands with small, short fingers; and dry skin. Her heart dilated to the right and to the left. The mother had diabetes. Both parents were extremely fat, as was the patient herself. Menstruation was regular but scanty. She had one child. Thyroid treatment had a good effect. The serum contained a very large quantity of proteins; the carbohydrate tolerance was increased; the electrocardiographic findings were typical, as described by Zondek in myxedema (see Endocrin., 1920, **5**, 369).—J. K.

(THYROID) Causes, types and treatment of goiter (A contribution to the geographical surgery of the goiter in the Main river country) [Ueber Typen, Ursachen und Behandlung des Kropfes (Ein Beitrag zur geographischen Chirurgie des Maingau-Kropfes)]. Klose (H.), Med. Klin. (Berl.), 1921, **17**, 773-775.

Clinical experience has shown that the various forms of goiter correspond with the respective geographical areas within which the several types are found. The author distinguishes 2 types: (1) Highland thyroids with usually considerable degeneration, few blood vessels, and no nerves; the normal parenchyma is diminished to a minimum, thus often causing symptoms of hypothyroidism; (2) low-country thyroids with less degeneration and no hypothyroidism, but often slight hyperthyroidism. Goiters of the Main country (in the vicinity of Frankfurt) are of these two types. The author considers iodine therapy pernicious in these goiters because it causes augmented discharge of colloid.—A. B.

(THYROID) Malignant goiter (Die Struma maligna). Klose (H.) & Hellwig (A.), Klin. Wchnschr. (Berl.), 1922, **1**, 1687-1691.

Among 655 goiters operated upon by the author, 20 were malignant (17 women, 3 men). In 18 cases the tumor was a cancer; the other 2 cases were sarcomatous. Trauma seemed to be an important factor in pathogenesis, especially in operations for goiter, and incarceration of substernal tumors had no influence. Nine patients showed metastases in the lungs; 16, in the skeleton. Cachexia was never seen. When the case is properly diagnosed in

the beginning, complete ablation followed by x-ray therapy is the best treatment. When the tumor shows infiltration into the surrounding tissues, however, x-ray treatment alone (exact measuring is important) is preferable.—J. K.

Effects of thyroxin, THYROID extract, and sodium iodide, respectively, on neuro-muscular activity in cretin sheep. Liddell (H. S.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20**, 197-198.

Thyroxin was given to 4 cretin sheep and the spontaneous activity studied. There was a latent period of 3 to 10 days followed by a sharp increase in activity. With sodium iodide there was no increase, while with thyroid extract the increase was not marked by a sharp rise.—J. C. D.

Gastric digestion in HYPERTHYROIDISM. Lorenzi (A.), Gaz. d. osp. e d. clin. (Milan), 1922, **43**, 660-661; abst., Presse méd. (Par.), 1922, **30**, 1026.

The idea that digestive function is related to the functions of the thyroid goes back to the time of Eppinger. Since then, various and contradictory results have been reported. Lorenzi carried out his experiments with the aid of the x-rays. Some gelatine capsules containing about 0.40 gm. of bismuth were ingested with an experimental meal. The author observed the moment of rupture of the capsules, and thus determined the time of gastric digestion. In the hyperthyroid patients this process seemed to be more rapid than in the normal subjects. This is explained by the fact that the major part of the functions of the stomach are regulated by the vagus which is functionally in relation with the thyroid.—R. G. H.

(THYROID) Discussion on the medical and surgical treatment of Graves' disease. Mackenzie (H.) & Berry (J.), Proc. Roy. Soc. Med. (Lond.), **45**, Sect. Clin. 1-62.

This lengthy symposium is an important though timeworn debate regarding the respective virtues of surgical, x-ray and medical treatment of Graves' disease, without, in the end, deciding specifically which treatment deserves the medical public's complete confidence. It is only possible, in an abstract, to detail the following salient points of the discussion:

Mackenzie states that though medicinal measures are valuable, there is no specific that the internist might use in Graves' disease. The elimination of infectious foci and a fair trial wth medicinal measures result in recovery of many patients, but in some cases surgery or the x-rays must be employed. Thyroidectomy results in marked improvement, and though the eyes still remain prominent, the frightened look usually disappears. Many patients require two or even three operations. Contra-indications to thyroidectomy are:

(1) fear of the operation; (2) mental symptoms; (3) diabetes; (4) auricular fibrillation. X-ray treatment of Graves' disease is successful in many instances, but local scarring, keloid and burns may result from irradiation. The main drawbacks to this treatment consist in the long time required to affect improvement and the difficulty of carrying it out in severe types of the affection.

Barry holds a less sanguine view of the advantages of operation on patients with Graves' disease, because of the tendency to relapse even after the most successful thyroidectomy, and the incompleteness of the cure in many cases that at first sight seem most favorable. Even when performed under the best of conditions, the removal of a hyperplastic goiter involves considerable danger to life —far greater than that of operations for simple goiter. The mortality is at least 3 to 5%, and in many quarters it is far higher. But even a 5% mortality is willingly faced by patients if the operation offers a good chance of cure. The inclusion into surgical statistics of toxic adenoma is misleading. Berry does not approve of operation upon patients who are improving and who do not feel ill, nor does he operate on unwilling patients. He does not approve of "stealing the gland," as he deems it much better to have the patient thoroughly cognizant of what she is to expect. Many patients who have made apparent recovery from the operation and are practically well for a considerable time may relapse or even die of the disease. In some of these a second operation is advisable, but there is a limit to the amount of gland that can be removed, lest the ultimate condition of the patient may be as bad as, or even worse than, the first.

Dunhill states that death is not the only tragedy in Graves' disease. Jessop has collected 25 cases and reported 2 in which an eye had been lost, due to ulceration because of extreme exophthalmos. Operation is not to be entertained until (1) the removal of infectious foci has been effected, (2) the patient has had a period of rest, and (3) symptomatic drug treatment has been given a fair trial. If no improvement occurs after a reasonable time, other measures such as x-ray and operation must be considered. In Dunhill's experience, x-ray treatment is unsatisfactory because it fails to improve the pulse rate, the size of the thyroid, the exophthalmos and the tremors. Again, it produces marked fibrosis in the gland, a process which continues long after the application of the rays, leading to the danger of myxedema. Untreated, some patients recover. Other patients are in various grades of ill health down to the most complete bed-ridden wrecks. Some can do light work, others require considerable rest between activities. Still others, very ill, are possessed of a spirit of restlessness. Again, some are waterlogged from cardiac and renal insufficiency. In still others, an eye is irretrievably damaged. In all of these, improvement under treatment would take years to affect, and in some, improvement is impossible. Most of these patients could be tremendously improved

by operation. Still, Dunhill never operates on a patient with Graves' disease without fear and great anxiety, a feeling which does not leave him until some days after the operation.

Hale-White mentions the case of a woman who was admitted to the ward for operation on exophthalmic goiter. After she had been in a few days, and before the operation, evidence of typical typhoid fever was observed. She was transferred to the medical ward, and under the rest in bed got completely well of her exophthalmic goiter. Hale-White states that the presentation of a few cases recently operated upon is no proof that operation is best, for it is quite as easy to show similar results without operation. At least a hundred patients operated on and followed up for twenty years would have to be shown before definite conclusions as to the efficacy of surgery could be drawn.

Florence Stoney states that she has collected 200 cases of primary Graves' disease and of the syndrome superimposed upon an old bronchocele, all treated by x-rays. Of these, 78 are quite cured and strong up to 13 years after treatment; 1 is slightly myxedematous; 66 are improved and working, though possessing such symptoms as overstrained heart and other manifestations; and 21 are no better. Since treatment, 10 have died. Of the 200 cases, 185 are women and 15 men—the latter cases due to war conditions. The principles of treatment consist in a lessening of the thyroid substances and the removal of the cause. X-ray treatment can accomplish all that surgery can do, with the great advantage that the dose can be graduated so as to destroy the exact amount of tissue desired. Further advantages are the absence of shock of repeated operations, no risk to life and no pain. There are but three disadvantages of x-rays: (1) The improvement is slow, but this could be overcome by an early diagnosis and the early institution of treatment; (2) the possibility of telangiectasis, but an earlier institution of treatment and expertness of application would lessen its occurrence; (3) scarring of the neck; this, too, could be avoided. Stoney urges an early diagnosis when the patient might be "merely run down" with a rapid pulse and a rapid toneless first sound in the heart resembling the second. This is a strong indication of thyroid trouble, and if treated as such would save many patients months of illness. There are other difficulties connected with these patients: (1) the inability to alter the course of their lives; (2) the difficulty of removing mental worry; (3) the presence of exhausting brain work; (4) the presence of old bronchoceles which are liable to break down frequently.

Romanis states that thyroidectomy improves but does not cure the patient. Though there is an increase in weight, a lowering of pulse rate, and an improvement in the heart action, the pulse rate does not reach normal, the heart is still dilated, and the eyes still present exophthalmos. Even multiple operations do not produce

complete cure. In the few cases in which he deliberately removed the entire thyroid gland, the physical signs did not completely disappear. He asks whether the parathyroids are not a physiological myth. Neither he nor other surgeons with whom he has spoken on the subject had ever seen any evidences of tetany arising from operation in which no attention was paid to the parathyroids and in which there had probably been a partial or complete removal of these glands. He is tempted to believe that, in man at least, the parathyroids do not play as important a rôle as the physiologists would have us believe.

Walton states that the surgeon does not see the medical successes because he is not brought in contact with them. He believes the disease is due to thyroid hyperactivity. Surgery is not to be attempted during the first six months of the disease, for medical measures may during this time prove beneficial. He does not believe x-ray treatment to be of much service in the treatment of this disease. He advises medical treatment also as a preliminary to surgical treatment, and in cases in which too little thyroid has been removed by the surgeon.

Hernaman-Johnson emphasized the fact that Graves' disease cannot be produced by thyroid feeding, but that the affection is probably produced through the sympathetic nervous system and all the endocrine organs. Since the precise cause of Graves' disease is unknown, treatment must be symptomatic and empirical. Surgery is symptomatic treatment, as it breaks one of the vicious circles constituting the syndrome. X-ray treatment is administered with the same idea, but roentgen therapy is productive not only of local results but constitutional benefits as well.

Joll states that a careful search of his patients for infectious foci leads him to conclude that there is no ground for believing that Graves' disease is caused by intestinal or any other type of toxemia. Though the diagnosis of the disease is not difficult, yet he sees many patients diagnosed as Graves' disease who are really suffering from encapsulated tumors. Joll advocates early diagnosis and early operation in practically all cases.

Williams states that operations on the thyroid gland are inadmissible in Graves' disease. The disease is not only not a hyperthyroidism, but is not a disease of the thyroid gland at all. Many patients with advanced stages of the affection present no enlargement of the organ. Exophthalmos is due to adrenal excess, and heart symptoms to thymus enlargement. Graves' disease is a toxemia in which all the members of the endocrine family are involved. Treatment consists in the discovery and elimination of the causal toxin, which in the large majority of cases is gastrointestinal in origin. The enlarged thymus is also responsible for many of the nervous symptoms by its pressure upon the pneumogastric, the sympathetic, and the phrenic nerves. The mental

symptoms may also be produced by the enlarged thymus because of interference with the drainage system from the brain. There is no more justification for the removal of a lobe of the thyroid in Graves' disease than there is for the removal of one kidney in diabetes.

Wilson agrees that exophthalmic goiter is not a disease of the thyroid gland; it is a neuro-glandular disease. At present the disease is being treated from without, but he hopes that it will soon be treated from within.

Berry, in closing the discussion, states that many cases prove the efficacy of irradiation. He regards a patient as cured when the nervous symptoms disappear and do not return; he pays no attention to the neck and to the eyes, though in many cases these show improvement.

Mackenzie, in the course of his closing remarks, states that medical treatment must not be underrated. The surgeon is not in position to pass judgment upon the efficacy of medical treatment in Graves' disease.

Throughout the discussion the terms hyperthyroidism and exophthalmic goiter are used interchangeably.—I. B.

(THYROID) Iodine in natural waters in relation to goiter. McClendon (J. F.), J. Biol. Chem. (Balt.), 1923, **55**, xvi.

McClendon burns foodstuffs in a bomb-calorimeter to prevent loss of iodine. Foodstuffs derive iodine from soils, and river water represents leachings from soils. In the Mississippi river system, in Minnesota, iodine averages 0.8 per billion and goiter 8 per thousand troops; in Missouri iodine is increased to 2 and goiter reduced to 4. A discussion of chlorine and iodine distribution is given. Rats fed KI show small thyroids.—F. S. H.

The application of results obtained in experiments on the hyperplasia of dogs' THYROIDS to the treatment of exophthalmic goiter (Graves' disease). Mellanby (E.) & Mellanby (May), Proc. Physiol. Soc. (Lond.), 1921-22, **55**, p. x.

The authors were impressed with the similarity in histological appearance and in therapeutic response between thyroid hyperplasia in dogs and in human beings. Results of dieting upon patients with Graves' disease were reported. When butter was added to a normal diet, the symptoms were intensified. There was an increase in basal metabolism, a diminution in weight, and an accentuation of the tachycardia and nervous phenomena. A diet so arranged as to contain a small amount of fat and 15 cc. of cod liver oil daily, with separated milk powder, porridge, bread, green vegetables, eggs and lean meat, yielded a reduction in basal metabolism, an increase in weight, and in a lessening of the tachycardia and restlessness. Working on the assumption that the action of the cod liver oil was

due to the iodine content, 6 to 9 grains of potassium iodide were given to some patients instead of the oil. After a period of reduced basal metabolism, the weight of these patients became stationary or fell slightly.—I. B.

(THYROID) Idiopathic MYXEDEMA in a man of 37 (Idiopathisches Myxödem bei einem 37-jährigen Mann). Meyer-Bisch, Klin. Wchnschr. (Berl.), 1922, **1**, 1765.

The disease began when the patient was 14. Treatment with thyroidin gave splendid success. The patient lost 37 kg. weight and his psychical functions rapidly improved.—J. K.

THYROID extract and experimental lesions of nutrition (Extrait thyroïdien et lesions de carence experimentale). Mouriquand (G.), Michel (P.) & Sanyas (R.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 214-215.—T. C. B.

Diets adjuvant and antagonistic to the dystrophic action of THYROID extracts (Les régimes adjuvants et antagonistes de l'action dystrophique de l'extrait thyroïdien). Mouriquand (G.), Michel (P.) & Sanyas (R.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 216-218.—T. C. B.

A case of THYROIDEAN strumous teratoma of the OVARY (Un caso di teratoma strumoso tiroideo dell' ovaio). Parodi (A.), Pathologica (Genova), 1922, **14**, 727-731 (November).

The author considers ovarian struma as a teratoma in which the thyroidean tissue is the only constituent or is more or less abundant according to the predominant development of the cells of either layer. He believes that the tumor is malignant or not according to the quality of its tissue. He claims that "ovarian struma" is too generical a term and prefers to follow the nomenclature of Norris and Proescher and call it "thyroidean strumous teratoma of the ovary."—G. V.

Studies in the Kottmann reaction for THYROID activity. Petersen (W. F.), H'Doubler (F. T.), Levinson (S. A.) & Laibe (J. E. F.), Arch. Int. Med. (Chicago), 1922, **30**, 386-396.

The author's conclusions, which adequately summarize the article, are as follows. In clinical cases of hyperthyroidism the Kottman reaction may return to normal after thyroidectomy. Fright, on the other hand, produced a positive reaction in two patients; in normal control patients who were subjected to similar trauma, but who were not frightened (one unconscious, one semiconscious, the other conscious and calm), the reaction was within normal limits. Experimentally it was found that thyroxin injections, irradiation and massage of the hypertrophied gland resulted in an increased protective property of the serum which becomes

manifested in the course of several days. The serum alteration is therefore not a direct one, but is evidently the result of alterations in cellular metabolism brought about by the increased thyroid activity. Other experimental procedures may alter the reaction (bacterial shock, peptone shock, trypsin ingestion, hemorrhage, irradiation of remote organs). In no case was the delay in the reaction comparable to that observed with exophthalmic serums and we do not believe that the alterations in the reactions observed under these experimental conditions will detract from the clinical usefulness of the test in the diagnosis and the control of the therapy of thyroid dysfunction.—H. L.

The Kottmann reaction for THYROID activity. Peterson (W. F.), H'Doubler (E. T.), Levinson (S. A.) & Laibe (J. E.), Tr. Chicago Path. Soc., 1922, **11**, 261-263.

See Endocrin., **6**, 740.

(THYROID) Case of laryngectomy following thyro-fissure. Ridout (C. A. S.), Proc. Roy. Soc. Med. (Lond.), 1923, **16**, 8-9.

Description of the case of a male, aged 51, in whom, at operation for carcinoma of the larynx, it was discovered that the left lobe of the thyroid was involved.—I. B.

The action of THYROXIN on the body weight and liver glycogen of the mouse (Untersuchungen über die Wirkung des Thyroxins. I. Ueber die Wirkung des Thyroxins auf Körpergewicht und Leberglykogen weisser Maüse). Romeis (B.), Biochem. Ztschr. (Berl.), 1923, **135**, 85-106.

The general conclusion derived from this study is that thyroxin produces effects on body weight, fat tissue and liver glycogen entirely analogous to those produced by thyroid gland administration. Certain differences in sensitivity to the compound were found in the various mice used which were not attributed to age, sex or weight differences.—F. S. H.

The rôle of the THYROID in anaphylaxis (Quelques remarques au sujet des notes présentées par L. Kepinow et A. Lanzenberg sur le rôle de la glande thyroïde dans l'anaphylaxie). Savini (E.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 235-237.—T. C. B.

The influence of partial ablation of THYROID and THYMUS (Uber die Wirkung partieller Entfernung von Thyreoidea und Thymus). Scheunert, Klin. Wchnschr. (Berl.), 1922, **1**, 1625.

In rabbits neither removal of half of the thyroid nor grafting of the thymus had any influence. In a young pig this operation, combined with castration, augmented the growth rate and increased the quantity of fat. Control experiments showed that whether the thymus was grafted made no difference in the results. The weight

of the animals that had been operated upon and of the controls became similar at the 100 kilogram stage. In one pig half of the thymus was removed; the animal became stupid and acquired thick skin, thick ears and long hairs.—J. K.

(THYROID) Studies of nephritis in children. I. Nephrosis. Schwarz (H.) & Kohn (J. L.), Am. J. Dis. Child. (Chicago), 1922, **24**, 125-159.

Epstein and Lande showed that in this type of nephritis the basal metabolism is lowered very much below the normal. As the patients improve, the basal metabolism approaches nearer the normal. The metabolism is always low when the cholesterol is high, and high when the cholesterol is reduced in amount. Schwarz and Kohn report that the use of thyroid extract seems to raise the basal metabolism in these cases and in many instances has a miraculous effect on the edema. They began their treatment with small doses of thyroid and controlled the increase by basal metabolism determination.—M. B. G.

Adenomata of the THYROID. Shephard (J. H.), California State J. M. (San Fran.), 1923, **21**, 16-18.

The repair and activation of the THYROID in the HYPOPHYSECTOMIZED tadpole by the parenteral administration of fresh anterior lobe of the bovine hypophysis. Smith (P. E.) & Smith (I. P.), J. Med. Research (Boston), 1922, **43**, 267-283.

The authors have investigated in the pituitaryless tadpole the structural and functional responses of the thyroid to injections of fresh bovine pituitary substance. Studies previously carried out on this form have shown that when the buccal hypophysis is ablated at an early stage the thyroid becomes atrophic and functionally inactive. These animals do not metamorphose. This failure of the thyroid has been corrected by the injection of anterior lobe substance; injections of the neural or intermediate lobe do not repair the gland. With a moderate dosage of anterior lobe substance the atrophic thyroid can be brought to a normal size (as determined by wax models) and structure, the specimens metamorphosing. With larger doses or with more certainty when only the middle part of the anterior lobe is used the thyroid becomes relatively enlarged and exhibits pronounced hyperplasia. Thus by varying the anterior lobe hormone it is possible to secure any type of thyroid from one displaying extreme atrophy to one displaying pronounced hyperplasia. The feeding of anterior lobe does not affect the thyroid. General body overgrowth and a pronounced darkening resulted from these injections in both the hypophysectomized (albinous) and normal tadpole.—Author's Abst.

(THYROID) Graves' disease, its pathogenesis and its treatment (De ziehte van Basedow haar pathogenese en haar behandeling). de Stella, Vlaamsch. geneesk. Tijdschr. (Gent), 1922, **3**, 658-664.

A general review without new data, offering inadequate evidence that Graves' disease is caused only by inflammation of the throat. The importance of emotions is denied.—J. K.

THYROXIN, its history, chemistry, and therapeutics. Stephenson (T.), Prescriber (Edin.), 1922, **16**, 334-339.

No new data.—F. C. P.

(THYROID) The metamorphosis of neotenous amphibians. Swingle (W. W.), J. Exper. Zoöl. (Phila.), 1922, **36**, 397-422.

Necturus does not undergo metamorphosis when fed, injected or engrafted with thyroid substance. The physiological activity of the thyroid substance used was demonstrated by using it on immature larvae of Rana clamata which underwent premature metamorphosis. Thyroids are present in necturus and may be shown to be physiologically active when engrafted into immature anuran larvae. It is evident that necturus has lost the power to metamorphose in response to stimulation by thyroid administration. Axolotl, on the other hand, responds readily to feeding or injection of thyroid. Axolotl possesses a large thyroid which, although incapable of producing metamorphosis in the animal itself, has a stimulating effect on the immature larvae of anurans. The same is true of the thyroids of large neotenous larvae of Rana clamata, which stimulate immature larvae of the same species. Four explanations are suggested for the failure of the thyroid to cause metamorphosis in these neotenous forms. They are: (1) defective blood supply for taking away the hormone; (2) a defect in the nervous stimulation which makes it impossible for the gland to release the hormone into the blood stream; (3) defective endocrine interrelations which prevent the release of the hormone; (4) or the presence of substances in the blood which neutralize the hormone.—M. M. H.

THYROID transplantation and anuran metamorphosis. Swingle (W. W.), J. Exper. Zoöl. (Phila.), 1923, **37**, 219-257.

The thyroids of Rana catesbeiana and Rana clamitans were transplanted into other larvae of the same species. The two forms used have a very long larval life and the object of the experiments was to determine the time at which the thyroids of these species become physiologically active. Glands were selected for transplantation at different periods of the larval life. It was found that while the thyroids of immature larvae do not cause an acceleration of development in the host, those from specimens having fairly well developed hind limbs will cause a slight hastening of metamorphosis and those from newly metamorphosed frogs will cause a greater

acceleration. The author concludes that in forms having a long larval life some activator of the thyroid is absent, and suggests that the hypophysis may furnish this stimulus in the species in which larval life is completed in a few weeks. Neotony would then be due to a defect in the interrelation between the thyroid and the hypophysis causing an inhibition of the secretory activity of the former gland. This is advanced as an hypothysis not directly supported by the experiments described in the paper.—M. M. H.

(THYROID) The value of basal metabolism in the diagnosis and treatment of CRETINISM. Talbot (F. B.) & Moriarty (M. E.), Am. J. Dis. Child. (Chicago), 1923, **25**, 185-197.

The basal metabolism of 10 cases of cretinism was studied. The determination of basal metabolism makes possible an early diagnosis of cretinism before the usual clinical symptoms appear, shows the correct standards to use in children in determining whether the subject is suffering from hypothyroidism, and is of distinct value in indicating the amount of thyroid which may be given with maximum efficiency. They found that the metabolism of a cretin is low as compared to that of the average normal child. It is possible to differentiate, by means of basal metabolism determination, between questionable hypothyroidism, cretinism and normality. The dosage may be regulated by the laboratory findings. Present evidence indicates that the total metabolism should be raised to the expected metabolism of normal children of the same age. Basal metabolic studies make a diagnosis of cretinism possible as early as 3 months of age. Better results should be obtained if treatment is started in the early months and persisted in. When the basal metabolism is normal in questionable cases, thyroid should not be given. The intermittent administration of thyroid produces variations in the basal metabolism. The average normal metabolism for the physical age of the patient must be reached before the best therapeutic results can be obtained.—M. B. G.

(THYROID) Surgical considerations of goiter. Terry (W. I.), Northwest Med. (Seattle), 1922, **21**, 324-328.

Terry classifies goiter into adolescent, colloid, toxic and non-toxic adenoma, and hyperplastic (exophthalmic goiter). He refers to the large goiter belt in the northwest United States and along the Great Lakes. The work of McCarrison in India on the relation of infection to goiter is mentioned. Prophylaxis of goiter by the administration of sodium iodine, as practiced on a large scale among school chidren in Akron, Ohio, is stressed. The author strongly emphasizes the clinical differentiation between adenoma and exophthalmic goiter. He believes that treatment of toxic and non-toxic goiter should be purely surgical and that there is no benefit to be derived from iodine, x-ray or other medical measures. He admits

that hyperplastic thyroids are occasionally improved by rest and x-ray radiation, but believes that such cases almost always relapse sooner or later and, therefore, should have surgical treatment early in the disease before the heart is badly damaged. In severe toxic cases he recommends implantation of radium emanations in minute capillary glass tubes as a preliminary step to lobectomy. He insists that the patient must have absolute confidence in the surgeon. It is sometimes necessary and advisable to "steal" the goiter without the patient's knowledge; if the patient does poorly during the operation it is wiser to stop, send the patient back to bed and complete the operation at another sitting; this will avoid many fatalities. Some subjects after operation have a high temperature of 106-107 degrees; this severe complication can sometimes be combatted by the liberal use of ice bags over the head, heart and body.—H. L.

The x-ray treatment of THYROTOXICOSIS. Trostler (I. S.), Illinois M. J. (Oak Park), 1923, **43**, 64-70.

A brief résumé of the etiology, symptomatology and diagnosis of toxic goiter, with a discussion of the rationale of x-ray therapy in thyroid hyperactivity. Trostler claims that when adhesions occur after irradiation, they are not due to treatment but to thyroiditis or some other cause. His reasons for regarding x-ray therapy in hyperthyroidism as the treatment of choice are as follows: because no harm can result, and past results show that the method has cured many and relieved all others treated; there is no operative risk; there is no confinement in bed; there is no fear of operation; there is greater likelihood of cure and less likelihood of recurrence, with the additional assurance that there are still the other methods of treatment if recurrence takes place; there is likelihood of a shorter period of disability; and there is no scar on the neck. In the author's experience, 4 to 8 full dosage treatments effect a cure. The **thymus** is also irradiated. In the presence of extreme toxicity, full dosage treatment is not administered at the beginning. In the average case a full dosage treatment is administered at intervals of about 21 days, the patient being kept under observation in the meanwhile. The author warns that the x-ray therapist must be as expert with the apparatus as is the surgeon with the scalpel.—I. B.

THYROID inflammation following parturition (Sur un cas d'inflammation du corps thyroïde dans les suites de couches). Vallois & Roume, Bull. d'obst. e. d. gynéc. (Par.), 1922, **11**, 662-663.

Two weeks after parturition the patient complained of fever and constriction of the throat. Tumefaction of the thyroid was found. Diagnosis was made of acute inflammation of the thyroid superimposed on a pre-existent goiter. Hot compresses were used as treatment, and recovery by simple resolution occurred.—F. S. H.

(THYROID) Graves' disease. Waller (H. E.), Prescriber (Edin.), 1922, **16**, 323-327.

The author concludes from his experience with 70 cases that Graves' disease is determined by the endocrine make-up of the individual (largely a hereditary matter), that it is usually secondary to some chronic infection, such as dental defects, tonsilitis, chronic nasopharangeal inflammation, rheumatism, colonic disturbance, or tuberculosis. Waller believes that surgery and x-ray treatment are necessary only in exceptional cases.—F. C. P.

(THYROID) Graves' disease and fibrinous bronchitis (Basedow'sche Krankheit und Bronchitis fibrinosa). Weber (H.), Med. Klin. (Berl.), 1921, **17**, 1143; abst., Schweiz. med. Wchnschr. (Basel), 1923, **53**, 127.

A case report. The author believes that vagus hyperirritability played an important part.—R. G. H.

Surgery of THYROID. White (P. A.), Iowa State M. Soc. J. (Des Moines), 1923, **13**, 11-15; cit., J. Am. M. Ass. (Chicago), 1923, **80**, 656.

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